[COMMITTEE PRINT]

COMMISSION ON THE FEDERAL DRUG APPROVAL PROCESS

FINAL REPORT

PREPARED BY THE

SUBCOMMITTEE ON NATURAL RESOURCES, AGRICULTURE RESEARCH AND ENVIRONMENT

AND THE

SUBCOMMITTEE ON INVESTIGATIONS AND OVERSIGHT

TRANSMITTED TO THE

COMMITTEE ON SCIENCE AND TECHNOLOGY

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*On assignment to Budget Committee for 97th Congress.

LETTER OF TRANSMITTAL

HOUSE OF REPRESENTATIVES,
COMMITTEE ON SCIENCE AND TECHNOLOGY,
Washington, D.C., May 19, 1982.

Hon. DON FUQUA,
Chairman, Committee on Science and Technology,
U.S. House of Representatives.

DEAR MR. CHAIRMAN: We are pleased to transmit to you the final report of the Commission on the Federal Drug Approval Process. The report represents the work and dedication of 26 individuals who, in the finest spirit of volunteerism, labored long and hard to produce this thoughtful document.

The history of the Science and Technology Committee's involvement with pharmaceutical issues dates back to 1977 when we first heard that some doctors here believed that they were at a therapeutic disadvantage to their foreign counterparts because the Food and Drug Administration (FDA) took too long to approve new drugs. In May 1977, we asked the General Accounting Office (GAO) to conduct an investigation of this charge of drug lag. When GAO reported back, our worst fears were confirmed: the availability of life-saving and life-enhancing new medications was being delayed because of regulatory intransigence.

Numerous oversight hearings were conducted by our respective subcommittees so that we could become better educated as to the causes of and the cures for the drug lag. Finally, in May 1981 we determined that the best way to develop a comprehensive set of remedies was to empanel an expert commission of diverse membership. We asked leaders from academia, government, industry and the public to deliberate and report back to Congress with a consensus document, and they have met that challenge with distinction.

The essence of the Commission report is that there are a variety of ways to expedite the approval of new drugs without compromising public safety. We believe that the recommendations are thoughtful and sound, and we applaud the Commission's important and timely contribution to the dialogue on ways to reform the drug approval process. We are particularly gratified that the Commission believes that needed improvements can be accomplished administratively and that no changes are needed in the Food, Drug and Cosmetic Act.

We wish to acknowledge our appreciation for the contributions of Vice President Bush and FDA Commissioner Arthur Hull Hayes, both of whom gave generously of their time and staff resources to aid the work of the Commission. We also wish to thank Jonah Shacknai and Thomas Grumbly of the Science and Technology Committee staff for the able guidance they provided to the Commission in helping it meet its Congressional mandate. Most importantly, we wish to give special thanks to the 26 commission members who worked relentlessly to create this excellent report.

It is our hope that the Committee on Science and Technology in particular, and the Congress in general will read well the report that follows. It is, we believe, an important document in our long struggle to make new and important drugs available to the American public at the earliest safe opportunity.

Sincerely,

JAMES H. SCHEUER,
Chairman, Subcommittee on Natural Resources, Agriculture Research and Environment.

ALBERT GORE, JR.
Chairman,
Subcommittee on Investigations and Oversight.

LETTER OF SUBMITTAL

HOUSE OF REPRESENTATIVES,
COMMITTEE ON SCIENCE AND TECHNOLOGY,
Washington, D.C., March 31, 1982.

Hon. JAMES H. SCHEUER,
Chairman, Subcommittee on Natural Resources, Agriculture Research, and Environment and
Hon. ALBERT GORE,
Chairman, Subcommittee on Investigations and Oversight

DEAR CONGRESSMEN: On behalf of the Commission on the Federal Drug Approval Process, I am delighted to present you with our final report and recommendations. We trust that this report fulfills the mandates established at the inception of the Commission.

The Commission is deeply grateful to both of you for your personal commitment to the cause of improved drug regulation. Through your work with the Reagan Administration, particularly Vice President George Bush, a bipartisan approach to change has been possible. The creation of this Commission and your continued support throughout its life have contributed significantly to a climate in which reform may now be implemented.

A particular expression of gratitude is due the Commissioner of Food and Drugs, Arthur Hull Hayes, Jr., M.D. He twice addressed us about current problems facing the FDA and the Reagan Administration's efforts to reform the new drug approval process. He encouraged the Commission's own work. We in turn wish him speed and success in his program.

Commission expenses were defrayed by the generosity of Project Hope and the organizations from which some members came.

Because of their convictions about the importance of pharmaceuticals to the health of all Americans, 25 individuals joined me in carrying out the Commission's work. Numerous plenary and small-group meetings have been held since the creation of the Commission in July 1981. This report represents our labors and our consensus, although any particular member may not fully agree with any particular issue.

We recognize that the submission of this report will not serve as an end to discussions of this vital area concerning public health. We anticipate, however, that our recommendations will contribute to the momentum for change. We also hope that the exciting dialogue that has begun among such diverse individuals, representing government, industry, academia, medicine, law, and the public, will continue in other ways so that our primary goal—enhancing the availability of new drugs for treating patients—can soon be realized.

Respectfully yours,

F. GILBERT MCMAHON, M.D.,
Chairman.

INTRODUCTION

The Science and Technology Committee has maintained an active interest in the Federal Drug Approval Process for the past several years. Information developed by the staff of the Subcommittee on Domestic and International Scientific Planning, Analysis and Cooperation (DISPAC) indicated that substantial delays existed in Food and Drug Administration's drug review. On May 9, 1977, Chairman James H. Scheuer (D-NY) requested that the General Accounting Office (GAO) conduct an indepth review of the drug approval process.

While the GAO was conducting its review, the Subcommittee held hearings in August 1978 and on June 19, 21 and July 11, 1979, on the FDA Drug Approval Process. These hearings provided additional support for the conclusion that there was a significant "drug lag" in the United States as compared with other technically advanced nations.

On May 8, 1980, GAO provided the Committee with its report entitled "FDA Drug Approval—A Lengthy Process That Delays the Availability of Important New Drugs" (HRD–80–64). The GAO concluded that the FDA approval process was unnecessarily lengthy and that it often took as long to approve a life-saving drug as to approve drugs of relative unimportance. This lengthy process, in GAO's view, delayed the benefits important drugs could provide to the public.

In releasing the Report, George Brown (D-CA) then Chairman of the Subcommittee on Science, Research and Technology, set forth the Science Committee's basis for involvement in this subject, noting that it was:

> * * * interested in this subject not only from its position of responsibility for general oversight of scientific research and development in our country but also because of the Committee's interests in innovation and productivity in the United States, and in the use and methodology of risk assessment in the regulatory decision-making process.

At the same time, Chairman Scheuer indicated the committee's future role in the drug approval area, stating:

> It is becoming clearer to me that the major problem is not the need for extensive legislation but the need for further oversight to see that deficiencies are corrected and FDA policies reflect a reasonable approach to bring new drugs expeditiously to our nation's millions of sick and suffering citizens.

To follow up on Chairman Scheuer's call for action, the committee held a series of oversight hearings in the 97th Congress. In addition, Mr. Scheuer, now Chairman of the Subcommittee on Natural Resources, Agriculture Research and Environment, requested GAO to conduct a follow-up investigation of FDA's efforts to reduce the processing time of new drug applications.

To further FDA's efforts to expedite its mission, Chairman Scheuer, in conjunction with Congressman Albert Gore (D-Tenn.), Chairman of the Science and Technology Subcommittee on Investigations and Oversight, convened a Commission on the Federal Drug Approval Process on July 21, 1981. The Commission was composed of 26 distinguished academic, government and private sector experts on drugs and the pharmaceutical industry. The Committee was charged with two primary missions:

1. To make recommendations how the FDA's procedures for approval of new drugs can be expedited with compromising public safety; and
2. To make recommendations on the development of cost effective post-marketing surveillance processes that can guarantee the quick withdrawal from the marketplace of drugs which cause significant adverse effects.

Funding for the Commission was provided in part by Project Hope. The House Committee on Science and Technology and the Food and Drug Administration provided substantial funding through inkind services.

The Commission met formally on a monthly basis convening in July 1981 and concluding in April 1982. In addition four subcommittees of the Commission met several times monthly throughout the tenure of the Commission.

The Commission presented the following report.

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The Commission on the Federal Drug Approval Process expresses its gratitude to Congressmen Albert Gore and James H. Scheuer for their sincere interest in the problems surrounding the availability of new drugs and for their encouragement during the tenure of the Commission.

The Commission also wishes to thank Vice President George Bush for his personal interest in drug regulatory activities, as shown by his letter of support for the Commission's work.

The Commission is particularly grateful to the Project Hope Foundation and to Dr. William Walsh, Executive Director, for generous financial support, without which this Commission could not have functioned. Moreover, Project Hope provided gracious hospitality and pleasant surroundings at Millwood, Virginia, for two Commission retreats.

The Food and Drug Administration deserves special acknowledgment for its cooperation and assistance throughout the Commission's activities. Without the agency's openness and sharing, the work of the Commission could not have proceeded. In addition to sending three liaison members, the FDA graciously asked many individuals to appear before or work with the Commission, and appreciation is due each:

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The Commission wishes to thank many other individuals who kindly gave of their time to make presentations that were very useful to the Commission's deliberations:

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The Commission is indebted to Cynthia B. Wong, who labored energetically with the Commission's writing committee in drafting and editing this final report, and to Frances Jones and Sally M. Boyd, who handled many administrative tasks.

Finally, the Commission expresses its appreciation to the respective organizations from which the Commissioners came, for enabling them to participate in this worthwhile endeavor. The expenses absorbed and administrative and clerical services provided by many of these organizations were substantial.

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REPORT OF THE COMMISSION ON THE FEDERAL DRUG APPROVAL PROCESS

OVERVIEW AND SUMMARY

The sick need safer and more effective drugs. No area of therapeutics exists where the available medicines are adequate to treat all patients. It is clearly in the public interest to encourage pharmaceutical innovation.

The search for new drugs has become increasingly lengthy, expensive, and complex. The numbers of new chemical entities entering clinical research and those ultimately approved for marketing have declined dramatically in recent years. Although the reasons for this decline are many and diverse, it is generally perceived that regulatory demands and delays within the United States drug review system are significant factors. Innovation may be encouraged, therefore, by improving the efficiency and productivity of the federal drug approval process and eliminating unnecessary regulatory burdens on drug development.

The goal of drug regulation is to protect the public health and safety. But it should also be recognized that the public is not well served if useful medicines are kept off the market. Indeed, every FDA Commissioner in the last decade has publicly acknowledged that the failure to approve important new drugs can be detrimental to the public health. Thus, the protection of public health and safety requires both caution in decision making and prompt action in approving new and effective drugs. Although the two goals are not incompatible, they do require careful balancing.

This Commission recognizes the considerable merits of the current drug review system. Drug regulation is necessary to protect the public health. Moreover, the fundamental premises underlying the drug approval process are correct:

(1) Drugs should be acceptably safe, in that their benefits should outweigh their risks.

(2) Drugs should be effective, in that they should produce the therapeutic effect claimed.

(3) Before being marketed, new drugs should be judged to be acceptably safe and effective by qualified experts on the basis of adequate and well-controlled clinial investigations.

Furthermore, the Food and Drug Administration (FDA) has performed well in reviewing drugs. The agency has justly earned an international reputation for quality and integrity. Hence, the challenge to the Commission was to search for changes that would enhance the speed and quality of the approval process while maintaining the existing level of protection of the public health.

From this perspective, the Commission considered the current provisions regulating the Investigational New Drug (IND) and the New Drug Application (NDA) system. The Commission interpreted its mandates as requiring a review of the total drug approval process, from preclinical trials through clinical testing to NDA submission and approval, for the purpose of making the process more efficient and faster. According to data presented to the Commission, the total time involved from synthesis of a new chemical entity to NDA approval averages around 13 years. This time encompasses the actual drug studies, the preparation of the IND and NDA submissions, and the review of the submissions by the FDA. The public interest will be served if any part of this time period can be shortened without compromising the safety and effectiveness expected of drugs.

The Commission's discussion approaches the drug approval system as though it had distinct components, with separate parts covering the IND process, the NDA process, and FDA management issues. The recommendations themselves, however, revolve around certain themes that cut across these distinctions. The Commission found its deliberations focusing on four central questions that recur in considering each component of the regulatory system:

(1) What scientific evidence is sufficient to conclude that a drug is safe and effective and who should participate in determining the sufficiency and meaning of the evidence?

(2) What documentation is necessary to be submitted to the FDA to support marketing or testing, and when should it be submitted?

(3) How should the resources of the FDA be most efficiently used in performing the agency's duties in the IND and NDA process?

(4) What style of interaction between the FDA and the pharmaceutical industry is best to ensure efficiency and quality in the drug review process?

The Commission's recommendations, although organized around the three separate components used in analyzing the approval system, indicate the interrelationship of these components and the consistency with which these four central questions arose. For example, the sufficiency of scientific evidence can obviously be assessed only in the context of individual drugs with judgments made by experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs. The extent to which experts can participate in the FDA's IND and NDA process depends first and foremost on the number of experts available to the FDA. The pool of experts now available is limited; the FDA is constrained in hiring full-time staff by ceilings on numbers of employees and salaries, while its access to consultants and advisory committee members has been restricted by a conservative interpretation of the conflict-of-interest statute.

With appropriate changes, the Commission believes that more experts could participate, and thus they could be involved earlier and more continuously in the course of developing important new drugs. This involvement could, among other things, avert clinical studies that are not needed for NDA approval, expedite review of research data, and enhance the quality of FDA decision making.

The second central question named above, regarding the documentation needed to undertake IND studies or to support an NDA, has a direct effect on the time and resources required to perform the FDA's review. Through classifying research into categories that have distinct regulatory objectives, the agency could clarify its own duties and needs, thereby simplifying the requirements for IND submissions. Additional streamlining of requirements for documentation can occur in NDA submissions and in interactions between the FDA and drug sponsors.

Increasing the productivity of the FDA -- the third central concern -- is a high priority in an era of limited resources. Although changes in management procedures might help, senior FDA administrators have stated that little further improvement in the agency's performance can be realized unless the system is altered:

> . . . the IND/NDA process continues to be plagued by backlogs and by review times that are too long. Those who work in IND/NDA reviews feel the pressure of their responsibilities, and volume overload only increases this pressure. The process is labor intensive and will always remain so. I believe both reviewers and management in the Bureau of Drugs increasingly recognize that we are nearing the limit of our capacity to improve through productivity gains. There are, of course, only two solutions to this problem: more people or policy changes that will lead to reduction of workload.1/

The Commission was able to identify a number of areas where the burdens on the agency could be eased without increasing risks to the public health. Certain categories of clinical research, for example, appear to be no less safe for the public than the routine use of new drugs in the practice of medicine; the FDA's review of this research might thus be reduced. Likewise, aspects of the NDA submission could be streamlined to facilitate the FDA staff's evaluation. Expanded use of outside experts may also reduce the agency's workload through its effect on the quality of NDA filings and reviews. Finally, agency activities in regulating the conduct of biomedical research and in preclearing generic versions of marketed drugs offer opportunities for further shifts in agency resources to the drug approval process.

The last central question, FDA's interactions with the regulated industry, is of crucial importance. The drug regulatory process may impede drug development

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1/ Crout, J.R.: "The Drug Regulatory System: Reflections and Predictions." Food Drug Cosmetic Law Journal 36(3): 106-119, 1981.

if sponsors perceive that the atmosphere in which they operate is hostile. The FDA's approach to drug review has frequently been characterized as intensely adversarial in nature. To some extent, of course, an adversarial atmosphere is natural between the regulated and the regulator. The attitudinal climate has in fact improved significantly in recent years, and the trends toward more cooperation between the FDA and industry are to be encouraged.

Nevertheless, the Commission believes that room exists for further improvements. In particular, the high degree of formality now attending all industry-agency contacts is not appropriate in some situations where a prompt and candid exchange of questions and answers would facilitate a review. The use of outside experts during the drug development phase of an IND as well as throughout the NDA review may also provide a positive attitude toward regulatory requirements. When disputes arise, they should be quickly and fairly resolved so that both the drug sponsor and the FDA staff can turn their attention to other matters.

The Commission concluded that improving the current system does not require amendment of the present Federal Food, Drug, and Cosmetic Act. But the Commission does believe that changes should be undertaken in FDA regulations, operations, and management practices. The FDA's implementation of the statutes, although well-intentioned, may have unnecessarily impeded the development and approval of new drugs. The FDA itself recognizes the need for internal reform in order to facilitate drug innovation and has long been working on revisions to its regulations and practices. The Commission applauds this commitment by the agency.

The Commission's recommendations for change must not be misread. In no way does the Commission suggest cutting corners to get drugs approved faster. Rather, the Commission's emphasis is on minimizing the time to test a drug scientifically and to review the resulting data in order to determine that the legal standards for safety and effectiveness are met. A faster drug review process does not necessarily mean lower standards. The public expects high-quality science at the FDA and safe and effective drugs on the market, and so does the Commission.

It is the Commission's firm belief that the time has come for action on reforming the new drug approval process. Further agonizing over these issues -- many of which have previously been discussed, debated, and analyzed and, to a great extent, are now beyond controversy -- will do nothing to enhance the availability of new drugs. On the other hand, the Commission recognizes that promising proposals may not yield the anticipated results. Any innovation in a system should be reviewed for effectiveness after it has been in place for a period of time.

In making its recommendations, the Commission acknowledges that many of the proposed solutions are not new and that no single recommendation will, overnight, have a major impact on the drug review process. The burdensome nature of the regulatory system was built up incrementally over many years. Similarly, improvements will come from a multitude of separate actions, the cumulative impact of which can be great.

The recommendations that follow are divided into Core Recommendations, which the Commission found to offer the most significant potential for expediting the development and review of new drugs, and Additional Recommendations, which will further contribute to an efficient process. The discussions in the rest of this report seek to present the background issues surrounding each recommendation and develop a rationale for the Commission's conclusions; this material is critical to understanding the Commission's intent. Further suggestions and proposals that amplify the Core and Additional Recommendations are also presented in the ensuing discussions. The headnotes in front of each recommendation below refer to the respective discussion sections.

CORE RECOMMENDATIONS

THE IND PROCESS: Early Clinical Research

- To permit more drugs to be tested more expeditiously, the preliminary requirements for introducing new chemical entities into humans (such as drug chemistry, animal toxicology, and protocol specificity) should be studied with the goal of simplifying them consistent with the protection of human safety.

THE NDA PROCESS: Application of the Standards for Drug Approval

- The FDA Commissioner should clarify through regulation the interpretation and application of the statutory and regulatory standards for establishing substantial evidence of the effectiveness of a new drug. Effectiveness should be found to have been demonstrated either by two -- or when appropriate, one -- adequately designed and well-controlled studies that individually provide the necessary substantial evidence of effectiveness or by the accumulation of data from adequately designed and well-controlled studies that taken together provide such substantial evidence.

THE NDA PROCESS: The NDA Submission and Its Review

- NDA submissions should be greatly streamlined. Summary presentations of data should replace the individual case-report forms. The clinical sections of NDA submissions should be designed to facilitate efficient review and should contain tabulations of all the data needed to assess the design, conduct, and analysis of the important studies; they should not routinely include the individual case-report forms or tabulations of every datum those forms contain.

THE NDA PROCESS: Utilization of Outside Expert Advice

- The system of new drug development and approval should be modified to afford a more significant role to experts from outside the FDA, drawn from the academic and government biomedical research communities. On the request of the FDA or the drug sponsor, outside expert consultants should be available both to advise in the investigational development of each new chemical entity or important new use of an approved drug and to participate in the review of its NDA.

FDA MANAGEMENT: Resources for the New Drug Review Process

- Congress and the Administration should ensure that the FDA has sufficient and stable resources to review and act promptly on INDs and NDAs.

FDA MANAGEMENT: Improving Interactions with Industry

- The FDA Commissioner should encourage the timely and equitable reso'ution of disputes regarding INDs and NDAs by ensuring that mechanisms appropriate for different types of disputes are in place and readily accessible. In particular, the Commissioner should expand on existing mechanisms and explicitly encourage their use. An ombudsman function should also be established in the Commissioner's Office, where administrative or procedural problems can be taken when they cannot be satisfactorily or promptly resolved with line management.

FDA MANAGEMENT: Tracking the Review Process to Ensure Timeliness

- The FDA Commissioner should be provided with timely information on the status of NDAs undergoing review. Toward that end, a computer-based system for tracking NDAs should be utilized to enable the Office of the Commissioner, as well as senior Bureau of Drugs management, to review regularly the status of NDAs and to report appropriate information to the Commissioner.

FDA MANAGEMENT: Conflict of Interest and Expert Advisers

- Barriers to the participation of the best qualified outside expert advisers in the drug approval process must be addressed. In particular, the FDA Commissioner should request from the Department of Justice a less restrictive interpretation of the federal conflict-of-interest statute than that issued in 1978.

ADDITIONAL RECOMMENDATIONS

THE IND PROCESS: Objectives of Investigational Drug Regulation

- The IND regulatory system should recognize three district categories of regulated activity based on the purpose of each activity: 1) basic research, 2) drug development, and 3) therapeutic use of investigational drugs. In each category, the regulatory requirements should be rationalized and revised to meet the public policy objectives appropriate to the category.

THE IND PROCESS: Clinical Development Studies

- The FDA should provide guidance to sponsors on the information needed from clinical development studies to support NDAs. On request, the FDA and outside experts should become more actively involved in the planning of clinical development trials.

THE IND PROCESS: Investigating New Uses for Marketed Drugs

- Studies undertaken by pharmaceutical firms involving previously approved drugs should generally be regulated in the same manner as clinical development studies.

- The FDA Commissioner should clarify the FDA's policy that the therapeutic use of approved drugs by licensed practitioners for medical indications not included in the drug's approved labeling is not subject to requirements for FDA preclearance of an IND submission. Moreover, a practitioner's investigational use of such drugs should similarly be excluded from IND submission requirements as long as it does not involve risks significantly greater than medical use in accordance with the drug's approved labeling.

THE IND PROCESS: Therapeutic Uses of Investigational Drugs

- Rather than the traditional IND system, procedures should be devised to permit the compassionate or emergency therapeutic use

of drugs in investigational status through simplified mechanisms that ensure consistency in decision making and minimal paperwork.

THE IND PROCESS: Preclearance of Clinical Research

- An experiment should be tried in which certain types of clinical research, such as early clinical studies, are precleared through either channel of a dual-channel regulatory system, in which the sponsor of a drug may select either the FDA or a nongovernment body that is subject to FDA standards and monitoring to review the IND submission.

THE NDA PROCESS: Application of the Standards for Drug Approval

- The FDA Commissioner should revise the agency's review procedures, consistent with the Congressional intent, to ensure that due weight be given in the approval process to the judgment of experts, including clinical investigators and medical specialists, as to whether the effectiveness standard has been met.

- Drugs should generally be considered for approval on the basis of judgments regarding the safety and effectiveness of the drug *per se*. Only in unusual cases should relative safety enter into approval decisions.

- Data on drug efficacy and safety derived from studies conducted in other countries should be given full weight as evidence in proportion to their quality. The routine replication of randomized controlled trials should not be required; rather, when relevant foreign trials are convincing in themselves, it should be sufficient for a sponsor to provide clinical experience in the United States to supplement the results observed abroad.

THE NDA PROCESS: The NDA Submission and Its Review

- To enable parallel review by the different disciplines in the FDA, NDA submissions should consist of separate sections covering

chemistry, pharmacology, biopharmaceutics, and clinical studies on the drug. In addition, the NDA should contain a draft Summary Basis of Approval for use by the FDA.

- Management of NDA review responsibilities should no longer be split among separate offices of the Bureau of Drugs. Each professional member of an NDA review team should be responsible to a single team leader with regard to productivity goals on that NDA.

- The FDA, in collaboration with industry and academic experts, should undertake a fundamental analysis of those portions of the NDA review process that have to do with chemistry, manufacturing controls, and biopharmaceutics, in order to delineate more clearly the information essential for review, revise the requirements accordingly, and establish better managerial oversight of these portions of the review process.

THE NDA PROCESS: Utilization of Outside Expert Advice

- The FDA Commissioner should seek the assistance of leading professional societies, universities, and other appropriate bodies in an effort to gain for the FDA the services of consultants who are among the most qualified experts in various fields of pharmacology and therapeutics.

THE NDA PROCESS: Postapproval Regulation of Drugs

- Because drug-specific postmarketing surveillance would generally not expedite NDA approval, it should only be required by the FDA in those individual cases when it is justified by the concerns raised by the drug involved. In all other cases, the FDA should continue to rely on the current systems of postmarketing surveillance to gather new information about a drug after NDA approval.

- Special postapproval studies should be used to obtain specific information about a drug that is important but not critical to an NDA

approval decision; the approval decision itself should not be delayed pending the additional data.

FDA MANAGEMENT: Resources for the New Drug Review Process

- In order to preserve scarce scientific resources, the Bioresearch Monitoring Program regulations should be reanalyzed, and requirements not critical to protect the integrity of the research process or justified by continuing regulatory problems should be eliminated.

- FDA inspections done under the Bioresearch Monitoring Program should focus on policies and procedures that produce the highest yield for the effort invested. For purposes of routine inspections, a short form should be developed.

- All prescription drug products, including generic versions of pioneer products, should be subject to premarket approval by the FDA for the protection of public safety.

- NDA requirements for generic versions of drugs originally approved after 1962 should be studied for the purpose of reducing the workload of NDA reviewers, particularly medical officers. The conflict between eliminating requirements that are not essential for the protection of public health, such as a full NDA, and ensuring the adequacy of economic incentives for drug innovation through appropriate mechanisms should be promptly addressed.

- The FDA should require in vivo bioequivalency testing for all generic versions of drugs originally approved after 1962, except where clearly unnecessary or technically impossible.

FDA MANAGEMENT: Improving Interactions with Industry

- The FDA should provide guidance to its staff to encourage all review personnel to conduct timely, forthright, and even-handed discussions

with sponsors of the significant issues that arise at any time during the IND and NDA review process. An atmosphere of mutual respect and professional conduct should be encouraged and maintained. Formal communications should be limited to situations where such formality is warranted.

I. BACKGROUND

The FDA is responsible for regulating the testing and marketing of all new drugs intended for human use in the United States. Its basic authority is embodied in the 1938 Federal Food, Drug, and Cosmetic Act and in the Drug Amendments of 1962. The 1938 Act charged the FDA with ensuring the safety of all new drugs before they are released to the market. In 1962, partly in response to the tragedies engendered by thalidomide, the Congress imposed the additional requirement that a new drug had to be shown to be effective as well as safe; the Amendments also expanded upon the government's authority to regulate clinical investigations of drugs.

Before a new drug can be marketed, the FDA must ensure that the drug is safe and effective for use under the conditions prescribed, recommended, or suggested in the drug's labeling. A "new drug," as defined by the statute, may be an entirely new chemical entity or an already marketed drug either in a new formulation or proposed for a new use. The sponsor of the drug must demonstrate its safety and efficacy through controlled clinical tests that are themselves closely regulated by the FDA.

Development of a Drug

The development of a new drug is undertaken by a sponsor, which can be a drug firm, a federal agency, or an independent investigator at, for example, a hospital, clinic, or research institution. The FDA itself does not test drugs. Development generally begins with the screening of a great many chemical compounds in laboratory animals to determine possible therapeutic activity. During these preclinical investigations, the pharmacological and toxicological properties of the agent are studied. For a variety of reasons, many of the agents screened are eliminated from further development at this stage.

When animal studies suggest that a compound may be therapeutically promising, the sponsor moves on to clinical testing, which introduces the drug into humans for the first time. The sponsor must submit to the FDA a Notice of Claimed Investigational Exemption for a New Drug. The FDA has 30 days to review the submission to ensure that the product is reasonably

safe for human subjects. If the FDA does not object, the sponsor may begin clinical testing after the 30 days.

Clinical studies are divided, at least in theory, into three phases. Early clinical research, often referred to as Phases I and II, involves the first administration of a drug to humans and can involve from a few up to 300 subjects. It is described in the following excerpt from the FDA's IND regulations (Form FD-1571, Item 10):

> Phase I starts when the new drug is first introduced into man -- only animal and in vitro data are available -- with the purpose of determining human toxicity, metabolism, absorption, elimination, and other pharmacological action, preferred route of administration, and safe dosage range; Phase II covers the initial trials on a limited number of patients for specific disease control or prophylaxis purposes.

At some point in the drug research process, a decision is made as to whether the drug offers sufficient promise to warrant Phase III trials in order to develop the product for marketing. Only about 10% of the drugs screened in humans proceed to this stage. In Phase III, research expands to focus on issues collateral to the questions of fundamental toxicity, pharmacological activity, and efficacy. These clinical development trials usually involve larger numbers of studies and patients and more formal, rigid protocols. Questions studied during Phase III include the safety and effectiveness of the drug in various conditions or patient populations or in long-term use, the types and incidence of side effects, the potential for interactions with other drugs, and other information useful for drug labeling. These trials may be controlled studies, noncontrolled studies, or a combination of the two and may involve over 2000 patients. Historically, Phase III trials have cost more money and taken more time than any other single component of the development process.

In practice, the lines of demarcation between the phases of drug testing are not always clear. A

study commonly described as a Phase I test may occur after Phase II -- or even Phase III -- has begun. Although the drug development process is discussed in terms of phases, in actuality development is a continuum of research not generally divided into neat stages.

The NDA Review Process

After completing the animal and clinical tests, the sponsor may file a New Drug Application with the FDA, seeking approval to market the drug. The NDA, which consists of numbers -- often hundreds -- of volumes, contains full reports of all investigations and statistical analyses performed to demonstrate the drug's safety and efficacy. Also submitted are a description of the drug's composition; the methods, facilities, and controls for the manufacturing, processing, and packaging of the drug; samples of the drug and its components; and a draft version of the proposed labeling. All NDAs are reviewed by the Office of New Drug Evaluation in the Bureau of Drugs by a team consisting of a medical officer, a pharmacologist, a chemist, a statistician, and other specialists. By statute, the FDA is required to approve or disapprove an NDA within 180 days, although this rarely happens. The 180-day period can be extended by agreement between the sponsor and the FDA.

In the long run, most NDAs (perhaps 90%) are eventually approved by the FDA, although final approval frequently comes after considerable time and negotiation and the submission of additional data.

Another important part in the drug review process is played by advisory committees, comprised of experts from outside the FDA who advise the agency on matters pertaining to new drugs. These standing committees are usually scheduled to meet at quarterly intervals. During the NDA review process, these committees consider issues primarily relating to the safety and efficacy of a drug and to make recommendations on specific questions relating to the NDA. Even though their decisions are not binding on the FDA, committee advice is almost always followed. The time between committee recommendations and agency actions, however, is often considerable.

Drug Innovation in the United States

Recent analyses of innovation in the United States pharmaceutical industry suggest that the industry's research output is declining and that it is relying increasingly on foreign innovations. According to data supplied by W.M. Wardell,[2/] several trends have become evident. First, after a decade of stability, the number of new chemical entities developed by the United States pharmaceutical industry and entering clinical development declined by nearly 50% in 1975 and has remained at the lower level since.

Second, the percentage of IND filings for new chemical entities originally developed in this country fell from approximately 80% in the mid-1970s to 66% in the late 1970s. Today, one-third of all INDs filed by United States firms are for new chemical entities that have been licensed or acquired compounds from other companies; of these drugs, over 30% are foreign innovations. Small American firms depend on drugs licensed or acquired from abroad for nearly 50% of their new chemical entity INDs, and large U.S. pharmaceutical houses, which until recently had not acquired many compounds overseas, now obtain more than 20% of their new drugs from foreign companies.

2/ Wardell, W.M., DiRaddo, J., and Trimble, A.G.: "Development of New Drugs Originated and Acquired by United States-Owned Pharmaceutical Firms, 1963-1976." Clinical Pharmacology and Therapeutics 28(2): 270-277, 1980.

Wardell, W.M., May, M.S., and Trimble, A.G.: "Recent Trends in United States Drug Development, 1977-1979" (abstract). Clinical Pharmacology and Therapeutics 29(2): 288, 1981.

Eisman, M.M., and Wardell, W.M.: "The Decline in Effective Patent Life of New Drugs." Research Management 21(1): 18-21, 1981.

Wardell, W.M.: Statement prepared for the House Subcommittee on Oversight and Investigations of the House Committee on Science and Technology, United States House of Representatives, at Hearings on Pharmaceutical Patent Life and Innovation, February 4, 1982.

It is widely believed that the approval of new drugs in this country takes too long, is wasteful of the resources of both the FDA and the pharmaceutical industry, delays the introduction of promising new therapies, and may contribute to the decline in innovation. According to Dr. Wardell, the total time for drug development, from synthesis of the molecule to NDA approval, doubled from 6.5 to approximately 13 years between 1964 and 1980; the time from IND filing to NDA approval is now about eight years.

In addition, the average effective patent life -- that is, the time remaining from NDA approval to expiration of the main patent -- has declined from nearly 14 years in 1966 to less than 10 years in 1979-1981. Most of this decline has stemmed from an increase in the clinical investigation time in the United States. Some of it is also due to the Patent Office issuing patents more rapidly than before.

The cost of developing a new drug has also increased substantially. According to one source,3/ the average cost of developing a new chemical entity through market approval may be $70 million. Pharmaceutical manufacturers are continuing to invest in research and development efforts, but it is believed that an increasing percentage of funds is going toward "activities related to requirements rather than on efforts to discover new drugs."4/

Although a burdensome regulatory process is often blamed for discouraging drug innovation, it is not clear that the reason is solely, or even primarily, because of the United States drug regulatory process. Rather than pursue that question, however, this

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3/ Virts, J.R.: "New Pharmaceutical Product Development: Reward versus Risks and the Public Interest.", Delivered to the 22nd Annual Canadian-American Seminar, Pharmaceuticals in North America -- The Public Interest, Institute for Canadian American Studies, University of Windsor, Windsor, Ontario, November 1980.

4/ "Developing New and Better Drugs for the Public. An Initial Assessment." Report of the First Keystone Workshop on New Drug Development, Keystone, Colorado, September 1981.

Commission concluded that it was more important to look for ways the regulatory system could be improved to encourage innovation while preserving its underlying safeguards.

Establishment and Activities of the Commission

The Commission on the Federal Drug Approval Process had its genesis in Congressional hearings on pharmaceutical innovation and federal regulation of drugs conducted jointly by two subcommittees of the House of Representatives Committee on Science and Technology -- the Subcommittee on Natural Resources, Agriculture Research, and Environment and the Subcommittee on Investigations and Oversight -- chaired by the Honorable James H. Scheuer and the Honorable Albert Gore, Jr., respectively. As a result of the hearings and of their long-standing interest in the drug review process, Congressmen Scheuer and Gore formed the Commission on the Federal Drug Approval Process on July 6, 1981, charging the Commission with studying the process of reviewing drugs in this country and making specific recommendations for improving it. The mandates of the Commission on the Federal Drug Approval Process were as follows:

(1) To make recommendations on how the investigational phase of new drug development can be expedited without compromising public safety.

(2) To make recommendations on how the New Drug Application process can be expedited without compromising public safety.

(3) To make recommendations on the development of a cost-effective postmarketing drug-surveillance process that can guarantee the quick withdrawal from the marketplace of drugs that cause significant adverse effects.

Congressmen Scheuer and Gore appointed Dr. F. Gilbert McMahon, Tulane University School of Medicine, to chair the Commission. Commission members were drawn from the pharmaceutical industry, the public, the medical and legal community, and academia, plus liaison representatives from the FDA.

A confluence of events occurring at the time that the Commission was established helped focus its direction and decision-making process. The FDA had

long been reviewing its existing procedures for approving drugs. In 1979, the agency published for comment a series of papers entitled "Investigational and New Drug Regulations Revisions -- Concept Document." Many interested parties, including the Pharmaceutical Manufacturers Association, filed comments on these papers and petitioned for additional changes in the regulations. In 1981, the FDA Commissioner's Task Force for the Review and Improvement of the Drug Approval Process was created; three members of the FDA Task Force also served as liaison to the Commission. Secretary of Health and Human Services Richard Schweiker appointed a Department-level committee to review the drug approval process from another perspective. Additionally, the 1980 report by the General Accounting Office, entitled "FDA Drug Approval -- A Lengthy Process That Delays the Availability of Important New Drugs," was being updated; in September 1981, representatives from the General Accounting Office detailed the newest findings to the Commission.

In reaching its recommendations, the Commission considered these simultaneous efforts as well as the reports and findings of earlier Commissions and working groups.

Although many Commission members had previously supported specific proposals for changing the IND and NDA process -- proposals that often appeared contradictory to those of other members -- the Commission was created with the intent of achieving consensus. The Commission thus began with the hope that, if consensus could be reached by such a seemingly disparate group, the recommendations would carry more weight and the task of implementing them would be easier. This report, then, is a consensus document, and individual Commissioners do not necessarily agree with every recommendation made. The Commission respects this right to disagree.

Between July 1981 and March 1982, the Commission met in Washington, D.C., and Millwood, Virginia, for 12 days of plenary sessions, including a four-day retreat, plus numerous smaller meetings and conferences among working groups. As the Commission tried to define the major problems and issues, a wide range of topics surfaced. During the first few meetings, however, it became clear that not all possible subjects could be given full consideration in the Commission's brief tenure and that the Commission's efforts should be focused

on those areas that had the greatest potential of expediting the IND and NDA processes without compromising public safety, as the Commission's mandates directed. Accordingly, a number of issues were given at least a cursory examination but are not dealt with in the body of this report.

The following material is divided into three parts, covering the IND process, the NDA process, and FDA management issues. This categorization, while logical from the standpoint of the development of an individual drug, is not meant to be definitive. As can be seen in the subsequent discussions, the issues are not neatly separated, nor should the recommendations be viewed as separate pieces. These recommendations in the aggregate form a broad and integrated approach to improving the federal drug review process.

In working together these few short months, the Commission has embarked on a process that should not end with the issuance of this report. In the first place, an exciting dialogue has begun -- perhaps for the first time in this type of setting -- among representatives of government, industry and consumer groups, physicians, academicians, lawyers, and the public. The atmosphere throughout was one of mutual respect, honesty, and common goals. It is the first forum in a number of years that has brought these various groups together to hammer out consensus. This exercise has been a rewarding one and may serve as a model for future projects.

Second, while severe time constraints forced the Commission into the hard and most significant issues first, it also meant that other important factors were not fully dealt with. Much more can be done in improving the drug regulatory system. Other bodies, some of which might be composed of persons representing the broad interests reflected in this Commission, should carry on the effort -- including, after a period of time, assessment of the changes flowing from the recommendations set forth in this report. It is the Commission's hope that these recommendations, together with the forthcoming recommendations from the FDA internal Task Force, the IND/NDA rewrite project and other reforms already begun by the FDA Commissioner, will serve not as the final answer but rather as a continuation in the search for an ideal drug regulatory system.

II. THE INVESTIGATIONAL NEW DRUG PROCESS

INTRODUCTION

Current IND regulations require the submission of detailed materials to the FDA before and during the conduct of clinical drug research. In addition, the FDA requires informed consent, IRB review, good laboratory and clinical practices, record keeping, and inspections. These regulatory requirements increase the cost and time of the drug development process for sponsors and thus affect research. It is therefore important to examine closely current FDA policies regarding IND submissions and other requirements affecting clinical research to see whether modifications could lead to greater efficiency without sacrificing the benefits of these policies.

Before addressing specific areas within the IND process that the Commission believes could constructively be changed, the history of investigational drug regulation is described with respect both to the types of research covered by regulation and to the public policy objectives sought through regulation. A restructuring of the regulatory system for investigational drugs is recommended so that the requirements relate more directly to the purpose of the clinical investigation -- basic research, drug development, or the therapeutic use of investigational drugs. Based on the premises set forth in the first section, additional recommendations are developed for streamlining the current IND regulations for different categories of research so as not to burden regulators and sponsors unduly while ensuring that the public policy objectives for each type of research are met. Also recommended, as an experiment, is a dual-channel approach to regulating certain kinds of investigational research. A related aspect, the FDA Bioresearch Monitoring Program, is discussed under the FDA Management section of this report.

A. OBJECTIVES OF INVESTIGATIONAL DRUG REGULATION

Following enactment of the 1938 Federal Food, Drug, and Cosmetic Act, the FDA issued IND regulations that required only certain labeling and record keeping

by the drug's sponsor. Neither the submission of a proposed clinical study to the FDA nor a review of the study by a party independent of the sponsor was required. In the Drug Amendments of 1962, however, Congress broadened the FDA's statutory powers over investigational new drugs and specifically authorized FDA preclearance of an IND submission and certain record keeping requirements and controls over drug distribution. Imposition of these rules was left largely to the FDA's discretion; the only mandatory change was that informed consent must be obtained from research subjects. Immediately thereafter, the FDA adopted previously proposed regulations requiring IND preclearance by the FDA and other controls over clinical research.

Since 1963, the IND regulations have been expanded in response to changes or problems perceived in clinical research on drugs. Criteria have been articulated for controlled studies and guidelines developed for the clinical evaluation of over 20 classes of drugs. Standards of "good practice" in preclinical and clinical studies have been set forth. The doctrine of informed consent has steadily evolved, and new approaches to the protection of subjects and assurance of ethical research have arisen; the most prominent new practice has been the introduction of local IRBs. Finally, the FDA's inspectional and enforcement activities have grown significantly. As today's regulations consist of a series of individual changes made over time, the Commission decided that its review should address the entire IND regulatory process and not just its component parts.

Content and Review of IND Submissions

The FDA has described the IND process at length. Although the following statement originated in 1974, it remains among the most complete agency discussions of the contents of the IND submission and the review procedure:

> The original IND must include the structural formula of the new drug, control and manufacturing data, [curricula vitae of the] clinical investigators participating in the study, a protocol outlining the planned investigation, and other data and information. . . . The IND is

accompanied by data (generally animal data) supporting the safety of the drug under study for the proposed dosage and duration of administration for the original IND. Changes in design or implementation of an ongoing study must be reported to the FDA as an amendment to the IND.

After the sponsor submits his original IND, he must wait 30 days prior to the initiation of clinical trials with the investigational drug. During this period, the FDA has the opportunity to review the IND with respect to important safety problems and to request modification of the study or to request the sponsor to continue to withhold or to restrict the use of the drug in human subjects.

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If research is allowed to start, sponsors are required to monitor the progress of the investigational study and submit progress reports to FDA at least once a year. They are also required to notify FDA immediately upon occurrence of an unexpected or severe adverse reaction. Where there is an unexpected or serious finding in human subjects or in continuing studies on animals, a determination is made as to whether the human studies should be permitted to continue or if special laboratory tests or safety studies need to be undertaken.

In addition to the reviews of individual submissions to the IND, the IND is reevaluated as a whole on at least three occasions: (1) at the completion of preliminary studies to determine human toxicity, metabolism, absorption, elimination, and other pharmacological action, preferred route of administration and safe dosage range; (2) at the end of studies which cover

the initial trials on a limited number of patients for specific disease control or prophylaxis purposes; and (3) prior to a proposed submission of an NDA. At these points, all data developed regarding the safety and effectiveness of the drug in all of the populations for which it is intended to be permitted on the market are reviewed.

On these occasions, the FDA and its outside experts and consultant reviewers confer with the sponsor of the IND. The agenda includes an overall review of studies and results to date, with decisions to be made as to the adequacy of the studies, the types of additional data which need to be gathered, and the adequacy of the protocols for at least the initial studies to be carried out in the subsequent phase.5/

Several points deserve emphasis. First, the FDA rarely denies permission for pharmaceutical companies to conduct the studies they propose. Thus, the current system has led to effective self-regulation; IND sponsors and clinical investigators, in anticipation of the FDA review, have undertaken the necessary internal procedures to ensure the safety of subjects in early research. Second, after the original IND submission, there are no further routine holds on a drug's development. The IND sponsor may begin a new study on filing the pertinent protocol, although the FDA can suspend a new trial if necessary. Again, the system depends principally on the private sector to ensure the safety and quality of the additional research. Third, IRBs review proposed studies for ethical acceptability and the adequacy of informed consent documents. The FDA usually intervenes only in extraordinarily sensitive situations, such as

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5/ Statement by FDA Commissioner Alexander M. Schmidt, in Regulation of New Drug R&D by the Food and Drug Administration: Joint Hearings before the Subcommittee on Health of the Senate Committee on Labor and Public Welfare and the Subcommittee on Administrative Practice and Procedure of the Senate Judiciary Committee, 93d Cong., 2d Sess. 208, 1974.

those surrounding research on fetuses, children, and prisoners. Finally, in making risk-benefit assessments throughout the investigational life of a drug, the FDA evaluates the risks, potential benefits, and alternatives to the drug's proposed use in a specific disease or condition, in order to determine whether investigators may be permitted to have access to the drug for that use.

Types of Clinical Investigations

The clinical use of drug products not approved for marketing can be classified on the basis of either the sponsor of the research or the purpose of the research. The four types of sponsor are a commercial manufacturer, a government agency (such as the National Institutes of Health), a nonprofit organization (such as a medical school), and an individual medical practitioner. A majority of INDs are submitted by individual investigators, usually associated with an academic institution, who are called investigator-sponsors. Although investigator-sponsored INDs rarely lead to an NDA, the FDA indicates that they constitute a significant demand on the agency's scientific resources.

Categorizing clinical research according to its purpose, rather than its sponsor, is more useful for this discussion because it lends itself better to an analysis of the public policy objectives in regulation of clinical research. The Commission chose to classify research into five types of investigations: early clinical research, clinical development studies, new uses of marketed drugs, therapeutic uses of investigational drugs, and other biomedical research. A brief description of these five categories follows.

Early Clinical Research and Clinical Development Studies

Early clinical (Phase I-II) research and clinical development (Phase III) studies were described in the Background section of this report. Because drug research is a continuum, rather than a series of neatly defined steps, the terms "Phase I," "Phase II," and "Phase III" will be avoided in this discussion. Rather, the term "early clinical research" is used to cover basic research on a new drug -- that is, clinical pharmacology (in normal subjects and in patients with the disease or

condition to be treated) and the earliest very rigorously controlled effectiveness trials, often conducted in in-patient settings. Similarly, the term "clinical development studies" describes the later investigations undertaken for the full development of a drug in preparation for marketing.

Investigating New Uses for Marketed Drugs

Development activities may occur after a drug is originally marketed in a particular dosage form for a particular indication. Although these activities are lumped under the term "new uses for marketed drugs," the actual purposes of this research can include the following:

(1) Testing new indications for therapeutic use, such as a drug approved for angina that is now proposed for hypertension. These indications can be divided into (a) those where the drug is to be used within the range of dosage and duration already approved (for example, an approved dosage of 100 mg/day/2 weeks versus a proposed dosage of 50 mg/day/2 weeks) and (b) those where the drug is to be used outside the range of dosage or duration already approved (for example, an approved dosage of 100 mg/day/2 weeks versus a proposed dosage of 200 mg/day/long-term).

(2) Testing new dosage forms of the drug using either (a) the same route of administration (for example, an approved tablet versus a proposed elixir) or (b) a different route of administration (for example, an approved tablet versus a proposed intravenous injection).

(3) Testing the use of a drug with another marketed drug, either (a) as concurrent therapy (for example, one dose/day of drug A with three doses/day of drug B) or (b) in a single dosage form (for example, 50 mg of drug A with 100 mg of drug B in one capsule).

(4) Testing generic versions of a marketed product; approximately 15% of all INDs are in this group.

These drug development activities may occur at any time in a drug's commercial life, and the size, cost, and duration of the trials vary widely.

Therapeutic Uses of Investigational Drugs

This term covers situations in which an investigational drug (i.e., one not approved for marketing) is used by a physician primarily for therapeutic, rather than for investigational, purposes; that is, the principal objective is to treat a patient, and the collection of safety and effectiveness data is secondary. To accommodate this use within the IND system, the FDA has utilized a submission variously called "compassionate IND," "emergency IND," "service IND," "treatment IND," and "therapeutic IND." Three different categories fall under this heading:

(1) Drugs in preliminary research. During controlled trials on a drug in a particular condition, patients with that condition (or another condition for which the test drug may be effective) are encountered who cannot be successfully treated with any approved therapy. For various reasons, these patients cannot be placed in the ongoing trials, yet for them, the drug's potential benefits outweigh its risks. Thus for compassionate reasons, the FDA permits use of the drug. In some cases, the drug is first requested by a physician when the patient is in crisis, and the FDA permits emergency use to precede the required paperwork.

(2) Drugs acceptable for marketing but not yet approved. There are two situations in which the FDA "knows" that a drug is safe and effective but approval is not yet possible. After controlled trials on a drug are completed, time is required to process the NDA. Until approval, noncontrolled trials generally continue. If other physicians learn of the drug and seek access to it for certain patients, the FDA may allow them to join the trials pending final NDA approval, again for compassionate reasons. Data generated at this stage may or may not be useful in the final approval and labeling decisions. In the alternative case, a drug is known to be safe and effective and could be marketed, but its medical use would be so rare that no commercial firm will sponsor an NDA. The drug may be supplied by a drug manufacturer or the federal government as a public service; for instance, the Centers for Disease Control provide drugs for certain tropical diseases, and the National Cancer Institute provides certain anticancer drugs. For these drugs, the FDA has allowed distribution under a service IND.

(3) Drugs not acceptable for marketing. In rare situations, an effective drug has been found unsafe for general marketing, either before it has been approved (for example, practolol) or after marketing experience (for example, phenformin and azaribine). For some patients, however, these risks will be outweighed by the benefits because they cannot be treated by other available therapies; in such cases, the FDA has permitted use of the drug under a compassionate IND.

Other Biomedical Research

This term serves as a catchall for human experiments involving chemicals that are deemed to be drugs because they fulfill the statutory definition of "drug" (i.e., they are intended for the diagnosis, mitigation, treatment, or prevention of disease) or that are not covered by the other categories, such as chemicals used to tag materials with isotopes for determining human pharmacokinetics or to induce a biological response.

The diverse studies in this category present unique policy questions, such as whether the FDA's mandate is to regulate only "drug" research or to regulate all experimentation on human subjects, therapeutic or not, that involves the deliberate exposure of people to chemicals. The risks from this research, the regulatory burden on the FDA, and the relevance to commercial drug development are not known. Because it has not been suggested that this area of research significantly affects the cost or speed of the new drug approval process, the Commission chose not to examine it further and accordingly it is not discussed further in this report.

Public Policy Objectives in Regulating Investigational Drugs

In looking at the history and evolution of the FDA's IND activities, the Commission identified eight public policy objectives that appear to be sought in the regulatory system: safety, the rights of subjects, ethics, scientific merit, integrity of the data, noninterference with the practice of medicine, facilitation of research, and readily ascertainable authorization. Before considering any changes in the system, it is useful to think about the relative significance of these objectives according to the different categories of research.

Safety

The health of research subjects should be protected. Narrowly stated, the goal is to avoid significant and unreasonable risks of death, illness, or injury. The protection of subjects has, however, also been interpreted as a broad risk-benefit standard in which risks (even if unidentified) are presumed always to exist. In reviewing clinical research, safety evaluations are always of foremost concern to the FDA.

Early clinical research presents unique concerns for safety because it constitutes the first use of a compound in humans. In clinical development trials, on the other hand, the risks are somewhat better defined because of the data obtained in the early trials. In addition, the subjects are patients suffering from the disease or condition sought to be treated by the drug, and they therefore may benefit from its use. Nevertheless, safety remains a consideration because alternative effective therapy is frequently available. Moreover, patients may also have other medical problems; the drug may be used for longer periods; and more people are exposed.

By the time a marketed drug undergoes study for a new use, its safety profile is much better defined. Novel issues of safety might, however, rise from an increase in dose or duration of treatment, a change in the route of administration, a drug-disease interaction, or a possible lack of effectiveness in the condition now being studied.

The therapeutic use of unapproved drugs involves an entirely different risk-benefit assessment. Subjects are always sick and commonly cannot be successfully treated with available therapies. Thus, greater risks may be acceptable.

The Rights of Subjects

The rights of research subjects should be protected, including the right of privacy and the right to give or withhold consent to participate in the research with adequate knowledge of its risks and alternatives. These rights are of equal concern in all categories of drug research. The FDA, however, rarely preclears informed-consent documents, deferring to IRBs.

Ethics

Research should be ethical. Not only should the scientific questions be legitimate, they should be worth answering; that is, the potential benefits from the study (to the participants or the public) should outweigh its risks. Moreover, the study should be compatible with prevailing social norms. The FDA generally defers to IRBs for ethical reviews of all proposed studies.

Scientific Merit

Research should be scientifically sound. Studies should be designed to answer legitimate questions and contribute to scientific knowledge. They should also be conducted by competent investigators. Further, the data to be obtained should be adequate to allow the sponsor to draw reasonable conclusions, and, in the case of studies intended to document safety and effectiveness, the data should be adequate for the FDA to make a decision on marketing approval.

The degree to which the FDA reviews studies for scientific merit should vary according to the type of research. Early research explores whether full clinical development is justified, and speed and flexibility are of prime importance at this time. Only about 10% of all IND drugs actually proceed to the larger development studies. Although the results from early research may help in the NDA approval decision, the critical data are seldom derived from these studies. Thus, the costs of having the FDA closely supervise the scientific quality of individual early studies are probably not justified by the benefits gained by the sponsor, the FDA, or society as a whole.

On the other hand, because the data generated in clinical development studies are central to the drug approval decision, scientific merit becomes a more significant concern. At least 80 to 90% of the drugs entering this stage eventually prove acceptable for marketing, although considerable time and resources are invested to assess the risks and benefits in greater depth and to define proper labeling. No one gains if avoidable deficiencies, such as in scientific design, are not prevented. In addition, if the yield of scientific information can be significantly increased

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with only marginal additional costs in time or money, sound public policy (as well as the ethics of clinical research) suggests that it should be.

Some studies investigating new uses of marketed drugs are clearly exploratory in the same way as early clinical research. Others are more akin to clinical development studies and thus present the same need for ensuring scientific merit. Still others appear more similar to the therapeutic use of an investigational drug, which may yield useful scientific data but by definition is primarily intended for patient care. This concern may preclude efforts to increase the adequacy and value of the data gained.

Integrity of the Data

The data derived from clinical research should be reliable. Inaccuracies and omissions may deprive the results of value and thus prevent any knowledge from being gained. This concern exists throughout types of research, but is heightened when the data are to be submitted to the FDA in support of an NDA.

Noninterference with the Practice of Medicine

Congress intended for drugs, not physicians, to be regulated by the FDA. Although drug regulation necessarily affects medical practice, the FDA tries to minimize the degree of interference. Therapeutic uses of investigational drugs may be medically appropriate. The compassionate use of investigational drugs has served as an important safety valve in the drug regulatory system, permitting access to otherwise unavailable drugs when justified by patient need. At the same time, preapproval promotion is restrained so that use of the drug in the guise of research does not pose public health problems or a potential for defrauding consumers.

The issue of the FDA's avoiding interference with medical practice rarely arises with regard to substances with no prior human exposure. For drugs in clinical development studies, however, the therapeutic use of an investigational drug commonly occurs, especially late in the development process as knowledge of the drug spreads. The problem becomes acute in the period just before approval, when marketing awaits only

final paperwork, and ebbs significantly when the drug has been approved and is readily available through conventional channels (unless the dosage form is inappropriate for the new use).

Facilitation of Research

Regulation ultimately harms the public health when it unnecessarily prevents or delays the development of new therapies. Although encouragement of drug research creates tensions with objectives such as subject safety and scientific merit, it is not incompatible with these other goals. Facilitating the development of new drugs benefits and promotes the public health. This objective applies equally to all types of research.

Readily Ascertainable Authorization

Drugs that lack accepted medical or investigational purposes should be excluded from interstate commerce. The IND and NDA system provides lawful channels for the development and marketing of new products. Those drugs found outside this system are presumptively violative and subject to seizure. To use this dichotomy as a successful regulatory tool, a means must exist to determine readily whether a specific drug in the hands of a specific individual has been authorized. Since 1962, the existence of an IND submission on file with the FDA has served this purpose.

Regulatory Mechanisms to Achieve the Policy Objectives

The objectives listed above do not necessarily require that the FDA preclear clinical studies. Indeed, some of the objectives are often attained wholly by means other than FDA review of IND submissions. For example, the rights of subjects and ethical standards are protected through the informed consent and IRB requirements; and the integrity of the research process and the resulting scientific data is ensured by standards of good practice reinforced by FDA inspections and audits. In the discussion that follows, it is assumed that these regulatory mechanisms will remain in place. The Commission is not recommending any significant changes in the existing requirements for informed consent, IRB review, or good laboratory and clinical practices.

Because the regulatory mechanisms available to attain the above objectives operate in different and overlapping ways, and because the specific public policy goals vary according to the purpose of the research, the Commission concluded that the preclearance requirements for drug research should not be the same in all cases. Regulatory controls for each category of study should be separately tailored to achieve the objectives sought. Of the five types of research discussed above, one (other biomedical research) has been excluded from discussion and another (new uses of marketed drugs) parallels the basic research and drug development phases for nonmarketed drugs. Accordingly, the types under discussion can be grouped into three categories for regulatory purposes.

- The IND regulatory system should recognize three distinct categories of regulated activity based on the purpose of each activity: 1) basic research, 2) drug development, and 3) therapeutic use of investigational drugs. In each category, the regulatory requirements should be rationalized and revised to meet the public policy objectives appropriate to that category.

B. EARLY CLINICAL RESEARCH

By identifying clearly the specific purposes for regulating early clinical research, it is possible to focus on what powers the FDA (or any other party acting under federal authority) should have to achieve these objectives while avoiding unnecessary regulations and burdens.

In the earliest stages of drug development, the primary public policy objective should be to protect the health and rights of the humans who may receive the investigational drug; the second goal is to facilitate the research process. Optimizing the scientific merit of a study is not an appropriate regulatory objective at this stage.

Because the health and rights of research subjects are largely protected by requirements other than the preclearance of studies, federal regulators need only the authority to stop a proposed study if it would expose participants to an unreasonable and

significant risk of illness or injury. In this context, "significant" risk does not include trivial risks or assumed but unidentified risks. The exclusion of insignificant risks from the risk-benefit assessment should foreclose regulatory efforts to modify the scientific design of a study in order to increase its potential benefits. The standard of "unreasonable" risk, on the other hand, recognizes that even significant risks may, in appropriate situations, be reasonable.

In the view of the Commission, simplification of preclinical requirements offers the most immediate opportunities to expedite early clinical research.

Drug Chemistry

Currently, an IND sponsor must submit information on the components and synthesis of its new compound. Although much is appropriate, some may not be (for example, detailed information on items such as the stability or the degradation products of the drug beyond the duration of the trial). Accordingly, the Commission recommends that requirements regarding drug chemistry and manufacturing controls be carefully reviewed and reduced to levels consistent with the safety determinations needed to justify early clinical research. Further information should not be required until the drug moves to large-scale testing.

Animal Toxicology

The FDA's present standards for preclinical safety studies have been developed over many years and are scattered among published papers, speeches, and draft guidelines. The Commission recommends that actual current practice regarding toxicology requirements be reviewed by a group of experts from government, academia, and industry, including clinical pharmacologists and others who use the animal data, to determine whether any types of toxicity tests may safely be postponed to later in the drug development process or omitted altogether; following this review, a single set of guidelines should be published. In reviewing toxicology requirements, the experts might compare animal data on previously tested drugs with subsequent human experience to assess the predictive value of preclinical testing.

Single-dose studies in humans can provide information not obtainable from animals, information useful in screening a series of related compounds for further development. Single-dose studies are now subject to the same requirements as studies in which doses are repeated over a few days, but the risks inherent in single-dose studies are probably different. For assessing safety, current requirements for single-dose studies appear excessive. These requirements are often costly and time consuming. For example, the requirements may compel the production of large quantities of the drug for use in animal studies. They also may mandate microscopic examinations of animal tissues even though these may not be scientifically justified because, for example, no abnormalities are observed either on gross examination or in carefully done clinical laboratory studies designed to evaluate the potential target-organ toxicity. The burden of these requirements has caused pharmaceutical firms to cut back on their single-dose human trials, and potentially useful drugs may never be screened in humans. The Commission recommends that separate, simplified preclinical toxicology requirements be developed for single-dose studies so as to allow for human trials of more drugs without increasing the risks.

Protocol Specificity .

The FDA now receives detailed protocols for each proposed early clinical study. Numerous amendments are therefore inevitable because of the iterative nature of this phase of research. Greater flexibility should be allowed in designing and modifying the general clinical plan and specific protocols for clinical studies. The FDA's regulations state the principle that should be followed (Form FD-1571, Item 10a):

> A general outline of [Phases I and II] shall be submitted, identifying the investigator or investigators, the hospitals or research facilities where the clinical pharmacology will be undertaken, any expert committees or panels to be utilized, the maximum number of subjects to be involved, and the estimated duration of these early phases of investigation. Modification of the experimental design on the basis of experience need be reported only in the progress reports

on these early phases, or in the development of the plan for the clinical trial, Phase III.

In summary, the general principle should be for federal authority to be limited to stopping a proposed study when the risks to subjects appear unreasonable and significant. By following this principle, nonessential regulatory requirements can be identified and should be eliminated.

- To permit more drugs to be tested more expeditiously, the preliminary requirements for introducing new chemical entities into humans (such as drug chemistry, animal toxicity, and protocol specificity) should be studied with the goal of simplifying them consistent with the protection of human safety.

C. CLINICAL DEVELOPMENT STUDIES

In the clinical development phase of drug research, it is also possible to identify the purposes of regulation and rationalize regulatory procedures. The public interest in the preclearance of proposed clinical development studies should be to protect the health and rights of the research subjects and to increase the likelihood that the research program will provide the information necessary to reach a decision on approval for marketing. To achieve these dual purposes the FDA should be prepared to offer assistance to sponsors who request it during this phase. The process should commence as soon as feasible after the drug sponsor is ready to proceed. The initial step should be, if no IND has previously been filed with the FDA, an IND submission describing the work done to date and the program for further clinical development.

FDA Guidelines and Advice to Sponsors

The FDA's use of guidelines for preclinical and clinical evaluations of drugs should continue as a means of informing sponsors and the public of current approaches to drug research. Preparing these guidelines, however, requires significant agency resources. Therefore, the Commission recommends that the FDA ask appropriate professional societies to develop or improve guidelines for specific classes of drugs. Many organizations might volunteer the expertise of their

members, who could work with the FDA and others to maintain guides to state-of-the-art testing. The FDA would, of course, retain the discretion to adopt each proposed guideline, thereby binding the agency to follow it. Freeing the agency of the drafting responsibilities, however, could both reduce the workload of scientific reviewers and lead to more useful guidelines.

The FDA should also confirm that its guidelines remain advisory and are not mandatory. A practice might be established in which any person -- drug sponsor or FDA reviewer -- who proposes a departure from the guidelines would be requested to explain the reasons for the change, so as to facilitate assessments of the proposal. This practice should not create a presumption that guidelines are binding the industry, although they are binding on the FDA under the agency's current regulations. Thus, the burden of justifying requests over and above the guidelines rests on the FDA. Accordingly, when an FDA reviewer asks for data or information in excess of that specifically required, the request should be approved by FDA supervisory personnel.

Currently, when the FDA has reservations about the design of a study but the deficiencies are insufficient to justify terminating the study, the agency sends a letter to the IND sponsor outlining the deficiencies. In these communications, the FDA does not differentiate clearly between those deficiencies that will render the study invalid in support of approval of an NDA and those that will not invalidate the study but, if corrected, would improve the scientific merit of the study. As a result, the agency appears to exercise more control over study design than perhaps even the FDA intends. The Commission recommends that, in the future, the FDA indicate in all IND communications which comments are considered critical and which advisory.

It should be emphasized that the FDA's involvement in study design should be advisory and at the request of the sponsor, who may accept or reject the agency's recommendations. Scientific pluralism should be preserved. The Commission believes that if the FDA does not agree with the design of a study, it nevertheless should not seek to stop that study unless the study presents an unreasonable and significant risk of illness or injury to the subjects or is so devoid

of scientific basis that it offers no possibility of yielding sufficient benefits to justify a risk to subjects.

IND Review and Planning Conferences

Upon the request of the sponsor, a pre-development phase conference (analogous to the current FDA end-of-Phase-II conference) should be held between the FDA and the sponsor. During this meeting, general guidelines and an overall plan for the development of the drug should be drawn up, including what kinds of studies are needed to show the safety and efficacy of the drug, how many subjects should be studied, and how best the data could be presented and analyzed in the NDA submission. Flexibility in study design, tailored for the drug in question, is the key.

This interaction should not, however, delay the commencement of trials unless there are significant and unreasonable risks to subjects. Indeed, it is more likely that, instead of a single pre-development conference, there will be several meetings as first the sponsor informs the agency of its plans and then, after the information is evaluated, the FDA provides its reactions. These interactions should occur for most prospective NDAs, if resources permit.

The kinds and details of information to be submitted to the FDA in anticipation of th s conference should be considered closely. On the one hand, the more detailed and complete the information is, the more fully the FDA can evaluate the proposed plan. On the other hand, excessive amounts of information increase the FDA workload and delay responses. It appears that the FDA contemplates receiving more information at this stage than may be needed (IND/NDA Concept Papers, pp. 15-17). A proposal made by C.N. Christensen, M.D., of Lilly Research Laboratories to this Commission deserves consideration; he suggests that the following information from the sponsor should be sufficient:

(1) A listing of the biopharmaceutic studies done or to be undertaken; it should be assumed that they will be done adequately.

(2) A listing of the clinical pharmacology studies undertaken, including a brief summary of each study, citing its purpose, the number of subjects

involved, the conclusions (but not all the results), and any adverse reactions.

(3) A listing and brief summary of the efficacy studies, including the design of the study, identification of the investigators, the number of subjects to be entered, the doses used and duration, the criteria of effectiveness, any adverse reactions, and the current status of the study.

(4) A full exposition of one pivotal study to show the format, the method for tabulating and summarizing the results, and the statistical analysis to be employed.

(5) Tables showing the number of patients to be included in the NDA, the doses and duration of treatment, and what data will be available from hematologic studies, urinalyses, clinical chemistry determinations, and special tests, such as EKGs, ophthalmoscopic examinations, or x-rays.

Involvement of Outside Experts

In discussing the NDA process below, the Commission recommends that, on the request of the FDA or the drug's sponsor, experts from outside the FDA be used more broadly in the development and approval process for most new chemical entities and important new uses of marketed drugs. For the reasons stated there, this approach would be most effective if the experts were selected at the time the drug entered clinical development trials. In this way, these experts could both gain familiarity with the drug and advise on its further development. They would be able to participate fully in the conferences between the FDA and the sponsor throughout the drug development phase.

- The FDA should provide guidance to sponsors on the information needed from clinical development studies to support NDAs. Upon request, the FDA and outside experts should become more actively involved in the planning of clinical development trials.

D. INVESTIGATING NEW USES FOR MARKETED DRUGS

Investigations on new uses for marketed drugs constitute the third category of research in which the FDA preclears studies. Here, too, the objectives of

regulation should be identified and regulatory requirements reviewed for appropriateness. The various types of research on marketed drugs can be divided into two subsets: those conducted by the drug's marketer and those undertaken by clinicians with no intention to market a product. The dichotomy between "commercial" development and "noncommercial" research serves better to focus policy formulation.

The public policy objectives regarding commercial activities in this area closely approximate those found in clinical development studies, while the concerns regarding noncommercial research parallel those in early clinical research. Generally, a phamaceutical manufacturer may be presumed to contemplate that the outcome of its research, if successful, will be used to support an application for permission to market a new dosage form or combination or to add a new indication to the labeling. On the other hand, noncommercial research will infrequently be used for those purposes.

Commercially Sponsored Research

Most studies proposed by a drug manufacturer on a marketed drug will be clinical development trials and should be reviewed by the FDA following the recommendations made above; that is, when requested by the sponsor, the FDA should hold a pre-development trial conference and outside experts should be involved if the planned new use is important. These steps will increase the likelihood that at the completion of the research, an approval decision on the new use (or new formulation or combination) can be made.

In certain situations, however, a manufacturer may conduct trials on its approved product that are not primarily intended to support an NDA filing. For example, the sponsor may conduct a preliminary study to detect activity for a new indication; if successful, the trial would later be superseded by the customary clinical development studies required to obtain an NDA. In another instance, the sponsor may carry out new research on the clinical pharmacology of a drug. These types of studies, analogous to early clinical research, should generally be regulated as recommended for that category of research.

- Studies undertaken by pharmaceutical firms involving previously approved drugs should generally be regulated in the same manner as clinical development studies.

Noncommercial Research

Ten years ago, the FDA announced that a medical practitioner "may, as part of the practice of medicine, lawfully prescribe a different dosage for his patient, or may otherwise vary the conditions of use from those approved in the package insert, without informing or obtaining the approval of the Food and Drug Administration." The agency further stated that the Federal Food, Drug, and Cosmetic Act "does not require a physician to file an investigational new drug plan before prescribing an approved drug for unapproved uses . . . ." 37 Fed. Reg. 16,503, 16,504 (Aug. 15, 1972). At the same time, the FDA encouraged physicians to submit proposed studies voluntarily for agency clearance. Although this announcement was intended to clarify the legal rights and duties of medical practitioners, confusion has persisted about when, if ever, their use of an approved drug outside the approved conditions for use must be specifically authorized by the FDA as part of clinical research regulated by the IND process.

As discussed earlier, Congress intended that the FDA regulate drugs, not physicians. Responsibility for the standards of medical practice has been left to the states and to the profession. Society has concluded that the public health risks, if any, created by physicians in routine medical practice -- including the prescribing of approved drugs -- do not warrant national regulatory controls.

By logical extension, investigator-sponsored and other noncommercial clinical studies on marketed drugs -- as distinct from medical use in a specific patient -- that pose risks to research subjects not significantly greater than the approved medical use of the drug should also be excluded from requirements for an IND submission. The rights and safety of subjects are protected by the informed consent and IRB requirements that are independent of FDA preclearance of studies. This type of research rarely yields scientific data for a later NDA decision, so FDA review will not expedite the drug approval process.

Noncommercial research that does not create risks substantially greater than approved uses includes studies that involve doses within the dosage and duration stated in the drug's labeling, the same route of

administration, and concurrent therapy with another marketed drug. In all these situations, the risks posed to patients are not significantly different from those already accepted by our society as part of the health care system.

Because the majority of IND submissions to the FDA today are investigator-sponsored, the elimination of a review requirement for those involving marketed drugs should reduce the agency's workload. It is an open question whether the FDA should decline to review this research even if voluntarily submitted. In an era of limited resources, the priority that the FDA gives to this type of research must be minimized, while reliance on professional standards, IRBs, informed consent requirements, and other controls not requiring intense FDA activity should increase.

Other research involving an approved drug's new uses may pose a significantly greater potential for injury to patients than use in accordance with approved labeling, for example, when it entails a new route of administration or a significant increase in the dosage or duration of use. Accordingly, this type of research should not be excluded from requirements for an IND submission to FDA; rather, it should be regulated in the manner recommended above for early clinical research. In both situations, the risks and public policy objectives are similar. In particular, the scope of FDA review should be limited to protecting the safety of human subjects.

- The FDA Commissioner should clarify the FDA's policy that the therapeutic use of approved drugs by licensed practitioners for medical indications not included in the drug's approved labeling is not subject to requirements for FDA preclearance of an IND submission. Moreover, a practitioner's investigational use of such drugs should similarly be excluded from IND submission requirements as long as it does not involve risks significantly greater than medical use in accordance with the drug's approved labeling.

E. THERAPEUTIC USES OF INVESTIGATIONAL DRUGS

The public purposes in regulating therapeutic uses of investigational drugs are often more subtle and complex than those raised in other areas. Safety

determinations, for example, now involve risk-benefit assessments of factors such as the seriousness of the disease, alternative therapies, the likelihood of successful therapy with the investigational drug, and the "freedom of choice" of patients in extremis. Scientific merit is a less important objective, although useful data might be obtained. Protection of subjects' and the public's rights in this area must also take into consideration the risks of deception or exploitation on the one hand and improper preapproval promotion on the other.

The therapeutic use of investigational drugs should be regulated in a manner different from those recommended for early clinical research and for clinical development studies. A distinct set of requirements should be developed with the objectives of minimizing regulatory burdens and reporting requirements consistent with ensuring safety. Informed consent, the ability to trace the drug to individual patients in the event of a newly discovered risk, and the reporting of adverse drug reactions, are examples of essential requirements, while detailed adherence to all good clinical practice standards would not be necessary.

A separate regulatory approach is needed in part because the availability of investigational drugs for therapeutic use is not widely known. Some physicians are aware of the compassionate IND system; others stumble onto it through personal contacts; many never learn of it. Patient care thus fluctuates for reasons unrelated to the needs of the regulatory process. The creation of a separate approach, with terminology to distinguish it from the present IND requirements, would greatly increase public awareness and allow all patients an equal opportunity to receive, in appropriate cases, investigational drugs.

The magnitude of the demands that full IND regulation of the therapeutic use of investigational drugs places on the resources of the FDA and the industry seems significant and disproportionate to the benefits of such regulation. It has been reported that most drugs awaiting NDA approval will, before approval, be subject to requests for permission to use outside the ongoing trials. Presumably, there is less activity surrounding drugs in preliminary research and drugs not acceptable for marketing, but some nevertheless exists. The standard IND rules create work that probably

is not useful in attaining the policy objectives. Documentation of investigations, protocol amendments, annual reports, inspections of investigators, and routine monitoring may be unnecessary and are generally less desirable than alternative requirements tailored to the particular situation.

Because the policy considerations differ depending on whether the drug is acceptable for marketing, is in preliminary research, or is not acceptable for marketing, the Commission recommends that these three categories be regulated somewhat differently from each other within the distinct set of rules for therapeutic use of investigational drugs. In no case would a manufacturer be required to participate; this discussion assumes agreement by the drug sponsor.

Drugs Acceptable for Marketing
But Not Yet Approved

Criteria are needed to determine when a drug is sufficiently close to approval that medical access to it should not be unduly restricted. By this time, the parameters of safety and efficacy are usually established. The process by which the FDA and the drug's sponsor decide to permit therapeutic use should remain simple and flexible but should become institutionalized (that is, clearly defined and subject to FDA management review to ensure consistency). Standard protocols should be prepared by the drug sponsor, who should be responsible for ensuring that physicians have appropriate qualifications to handle the drug and adequate information to use it properly. FDA-mandated IRB review for each physician enrolled is generally unjustified and quite burdensome; presumably, the drug will be marketed soon and no IRB involvement required. Useful data might be obtained from the study, but this possibility should be considered on an individual basis to avoid unproductive record keeping or reporting requirements. Restrictions on preapproval promotion and FDA monitoring of the sponsor's activities will be needed to prevent commercialization of a drug.

Establishment of distinct regulatory requirements for the therapeutic use of a drug awaiting approval should in no way offer disincentives for the prompt approval of the drug itself. Indeed, the efforts to expedite the approval of NDAs should decrease the need for compassionate INDs for drugs prior to approval.

Drugs in Preliminary Research

Different criteria should govern the therapeutic use of drugs whose safety and efficacy are not well defined. Accordingly, access to the drug should be more restricted than in the above situation, as to both when and to whom it is made available. Again, the decision-making process should remain flexible but be institutionalized within the FDA. It may not be possible to standardize protocols or even to provide adequate directions for use. IRB involvement is thus more vital and should be required.

Drugs Not Acceptable for Marketing

Risks and benefits are better established in the case of an effective but unsafe drug, often enough to make a decision regarding approval. The criteria for allowing therapeutic use of these drugs, however, are quite different from those applicable to the drug awaiting approval, because of the different risk-benefit ratio. The FDA's process of applying appropriate criteria to individual agents should be more formal than in the preceding categories, because the agency has already determined that the benefits of the drug generally do not justify the risks of its use. If therapeutic application is allowed without the drug's being marketed, a standardized protocol and labeling should be developed to specify the circumstances in which the drug has a favorable ratio of benefit to risk. In some situations, IRB review of individual cases may be appropriate.

- Rather than the traditional IND system, procedures should be devised to permit the compassionate or emergency therapeutic use of drugs in investigational status through simplified mechanisms that ensure consistency in decision making and minimal paperwork.

F. PRECLEARANCE OF CLINICAL RESEARCH

As described in the preceding parts of this section, a number of the public policy objectives in the regulation of clinical research are successfully attained through mechanisms other than the preclearance of individual studies by a party independent of the sponsor of the research, such as the FDA or an IRB.

The purposes uniquely served by preclearance involve the safety of research subjects, the review of scientific merit in the study for regulatory purposes, and the creation of a readily ascertainable authorization for each study.

Advantages and Disadvantages of Independent Preclearance

The primary disadvantage perceived in FDA review under the current IND system, or in any other situation involving preclearance of studies by a party independent of the sponsor, is that it can discourage research and innovation. As a result, the number of drugs tested in humans may decline, and drug research may shift to other countries where the regulatory system appears less burdensome. These perceived negative effects relate to factors inherent in the nature of independent review:

(1) Preclearance delays trials, although the amount of delay is not necessarily great. Currently, a sponsor may commence its initial studies 30 days after filing the IND submission unless the FDA imposes a clinical hold (which rarely extends more than 60 days from the submission). To this time, of course, must be added the time spent assembling the submission, any time the sponsor voluntarily delays the studies while awaiting substantive FDA comments, and any time required to obtain IRB approval.

(2) Preclearance introduces uncertainty into the research process. The fact that the FDA or any other independent body has choices as to what it can do (for example, to permit or delay a study or to request modifications in study design) creates uncertainty about what it will do with a specific proposal (although it may reduce uncertainty regarding the later acceptability of the resulting data). This uncertainty renders scientific and business planning more difficult. Any lack of consistency (such as among reviewers and divisions of FDA) can further hamper the prediction of outcomes.

(3) FDA or other preclearance of drug studies may constrain the autonomy of industry and academic scientists in designing their own research. It also creates a perception among these scientists that the reviewer is judging them on the quality of their scientific proposals, a perception that can lead to an adversarial attitude toward the reviewer.

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These three elements are intrinsic to any independent preclearance, whether by the FDA or someone else. The Commission believes, however, that the elimination of independent preclearance of proposed clinical research in order to overcome these three disadvantages is not advisable. Some party independent of the sponsor -- not necessarily the FDA -- should perform an evaluation before clinical trials are begun. This review provides several important benefits:

(1) Preclearance can prevent the use of a drug that is unduly risky or has not been sufficiently tested to define the risks. The independence serves to moderate the natural enthusiasm arising from a new discovery.

(2) An independent review can assess the scientific merit of the proposed research.

(3) Preparing for such a review is a disciplinary exercise for the sponsor to reassess both the risks and the scientific merit. As noted earlier, this internal review now serves as the primary screen for safety.

(4) An independent review provides other participants in the research -- investigators, institutions, and subjects -- additional assurance about the adequacy of previous tests; without it, some of these other participants might not participate until they conducted their own in-depth reviews.

On balance, the Commission concluded that the elimination of an independent review could compromise the safety of human subjects. Moreover, it might actually decrease the speed and efficiency of the drug development process, as suggested in the preceding paragraph.

Who Might Preclear Studies

The Commission therefore addressed the question of who might carry out the preclearance of clinical studies. Today, reviews are carried out both by the FDA and by local IRBs. The FDA's role is most important when a drug is first introduced into humans, because the animal toxicity data and chemical evaluations require an expertise not generally found in existing IRBs.

Later, however, IRBs take on the principal role, for although new protocols are filed at the FDA, they are not often reviewed before the study begins.

Several pharmaceutical companies and scientists in academia have vigorously urged the creation of a dual-channel review mechanism, in which a drug's sponsor can choose either the FDA or a nongovernment body (for discussion, this body will be called an Outside Review Board, or ORB) to conduct the independent preclearances now principally performed by the FDA. It is argued that an ORB would be more efficient and more responsive to drug sponsors and would possibly offer greater scientific expertise than the FDA. Independent from the government, ORBs would not be constrained by the restrictions imposed on the FDA regarding salaries, expenses, number of personnel, and facilities; they would also be free of other obligations, such as the review of NDAs and marketed drugs.

ORB preclearance of clinical research has, in fact, operated for six years in research involving radioisotope-tagged drugs. Under FDA regulations (21 C.F.R. § 361.1), approximately 100 Radioactive Drug Research Committees, composed of experts in this specialized field, exercise authority, together with IRBs, to regulate certain studies that would otherwise require an IND. The expertise, powers, and duties of these committees are specified by the FDA, which then monitors the work of the committees rather than the individual investigators or studies. The FDA receives only annual reports on the studies that were done; no notice is given the FDA for a study before it begins. This area of clinical research was deregulated because the risks to subjects under the circumstances permitted were foreseeably minimal.

The Commission recommends that this model be extended on a trial basis to other areas of clinical research where the safety of participants and other public policy objectives can be adequately protected without FDA preclearance of individual studies. At the same time, the FDA should continue to serve as one of the independent parties to whom drug sponsors may turn -- at their option -- for IND clearance. Thus, there will be two alternate channels for the review of clinical research. By having a choice, drug sponsors can, over time, determine whether ORBs are superior to the FDA. After the approach has been tried for some

time, its success can be evaluated and modifications can be made as appropriate.

The standards for ORBs might well vary according to the types of drugs being studied; indeed, it may be appropriate for the FDA to retain full control over the review of certain high-risk research. Where appropriate, however, the task of independent preclearance in specific areas of clinical research could be assigned to any organization competent and willing to perform it. ORBs could be created within the framework of existing institutions such as medical schools, or they could be free-standing, private organizations. In either event, they would be subject to FDA standards and inspections, so that the protection of the public's interests could be ensured.

The Commission emphasizes that it is not recommending that IRBs, as they currently are constituted and function, be used as the primary alternative to the FDA. For some areas of research (such as early clinical research), most present IRBs lack adequate toxicological, pharmacological, and chemical expertise to perform the type of review now done by the FDA. Moreover, IRBs have shown significant resistance to accepting the FDA's review responsibilities. (Much of this resistance can be attributed to a perception that the delegation will be imposed on IRBs without their consent. The recommendation is that the delegation may be accepted only in circumstances defined by the review body.) Undoubtedly, some IRBs have or would obtain the necessary expertise and might be interested in becoming involved in this project as ORBs. They, of course, would not be precluded from participation and, in any event, would continue to exercise their existing authority to protect subjects and evaluate ethical issues involved in clinical research. The structural relationships between IRBs and ORBs could take many forms, such as parent and sub committees, sister organizations, or totally independent bodies.

Skeptics of the dual-channel concept have raised important questions and concerns, the most serious one being whether ORBs would be superior to the FDA in both protecting human subjects and facilitating new drug research. This debate cannot be resolved ahead of time; the only way to determine the value of the dual-channel proposal is by an actual experiment.

A trial of ORB review would also provide other information relevant to the plan. The following have been suggested as potential problems: Multiple ORBs may create more inconsistency than is now found at the FDA (although it is likely that any one sponsor will work with only a few ORBs). A sponsor might shop around for a favorable reviewer. Confidence among investigators, IRBs, and subjects in the safety of proposed studies might decline. Substitution of ORBs could delay the research process more than the FDA now does. Logistical issues might arise, such as industry reimbursement of ORB costs, ORB liability for injuries to subjects, indemnification of ORBs by sponsors, confidentiality of commercial information, and the stability, continuity, and long-term viability of ORBs. There is a concern about the propriety of independent institutions serving as regulatory bodies in this area. Finally, the creation, standard-setting, and monitoring of an ORB system might impose significant new resource demands on the FDA.

Many of these potential problems are formidable, but they are not necessarily insurmountable, nor perhaps can they be fully resolved before the proposed dual-channel system is tested. Moreover, until the possibility of going forward is clear, there is little incentive to work out these questions carefully. Therefore, the Commission recommends that the FDA try, on a limited basis (perhaps for a certain period of time or for certain types of drugs), the establishment of a number of ORBs that would be allowed to review and approve proposals (in lieu of the FDA) in areas of clinical research, if they meet appropriate FDA-determined qualifications for those areas.

Types of Research Appropriate for ORB Review

The Commission does not believe that the dual-channel approach should be used for all clinical research. When the purpose of independent preclearance is largely to protect the safety of humans, ORB review might be acceptable. As long as the ORB is qualified to assess the risks of the study proposed, no significant reason exists to involve the FDA. ORB review is inadequate, however, for the purpose of ensuring that the scientific data are sufficient for NDA decision making. When the research will ultimately become part of an NDA, the FDA will at some point be asked to review

it anyway. Accordingly, ORBs could best be utilized for research that is clearly not, at the time begun, being done primarily to support an NDA submission.

Early clinical research, because it is not generally pivotal to an NDA decision, represents one category in which the ORB experiment should be tried. Historically, this area of research has been remarkably safe. The extent to which the FDA's actual review of research proposals (as opposed to the anticipation of such review) has contributed to this record cannot be assessed, but it is clear that few INDs are denied on safety grounds. FDA review at this stage involves physicians, toxicologists, chemists, and pharmacologists. These skills are present in teaching institutions, and experts could be enlisted to perform an FDA-style review of drugs proposed to be introduced into humans for the first time. ORBs that are willing to obtain the expertise and qualified to perform such reviews should thus be able to conduct them without there being any significant increase in risks to subjects. The other major public policy objective at this stage of drug development, facilitation of the research process, may be enhanced by ORB review. Similarly, qualified ORBs could review those areas of noncommercially sponsored research on marketed drugs that should not be excluded from regulation, as recommended above.

The most important phase of commercial drug development, the clinical development trials, should not be in the dual-channel system. It is very important that the FDA communicate its information needs and scientific questions to the sponsor throughout this phase, as well as during commercially sponsored research on marketed drugs. Although this interchange could be postponed and the review performed by an ORB, no advantages would accrue and potential losses might arise. For example, any uncertainty introduced into the research process by FDA preclearance is balanced by the sponsor's certitude concerning the relevance of the clinical development trials to its planned NDA. Likewise, the modest additional costs in time and effort to both the FDA and the drug company are preferable to the vastly greater costs if, at the end of the process, problems are encountered that could have been avoided. FDA involvement at this stage may affect the sponsor's perceptions of its autonomy over the research process, but confirmation of the FDA's advisory role as recommended above should diminish this problem. In

any event, deferral of contact between the FDA and the sponsor until the NDA submission might only produce even more heated confrontations over scientific questions at that time. Therefore, the Commission recommends that the FDA continue its exclusive involvement in large-scale clinical trials and commercially sponsored research on marketed drugs.

The dual-channel system is not necessary for regulating the therapeutic use of investigational drugs. For reasons stated earlier, this area should be handled through mechanisms other than those appropriate to clinical research.

- An experiment should be tried in which certain types of clinical research, such as early clinical studies, are precleared through either channel of a dual-channel regulatory system, in which the sponsor of a drug may select either the FDA or a nongovernment body that is subject to FDA standards and monitoring to review the IND submission.

III. THE NEW DRUG APPLICATION PROCESS

INTRODUCTION

At present, NDAs contain voluminous information regarding drug chemistry, pharmacology and toxicology, clinical studies to demonstrate safety and effectiveness, manufacturing processes and controls, and packaging, and labeling. The FDA review process involves staff medical officers, pharmacologists, chemists, biopharmacists, biostatisticians, and consumer safety officers. Additional help may come from other fields of science such as microbiology or nuclear physics. These professionals review the NDA to determine that it meets the statutory standards for approval. In reaching this decision, the FDA may consult with an advisory committee of experts in a particular area of therapeutics. At the time of approval, the agency may request further studies or data collection by the sponsor.

The entire process is labor intensive and time-consuming. The FDA and the pharmaceutical industry have long sought ways to expedite it. Until recently, the focus of the FDA's efforts was largely on better management of its personnel and procedures, and significant gains have been made along those lines. Further reductions in approval time will probably have to come from changes in more fundamental aspects of the NDA process.

The Commission believes that the NDA process can be improved and expedited, without compromising public safety, thro[illegible] reforms in three areas: the application of the standards used for drug approval, the materials necessary to support approval, and the process of decision making. The evidentiary standards for demonstrating the safety and effectiveness of a drug should be applied to reflect, within the intent of Congress, what the Commission believes are contemporary standards and practices in science. Requirements for the submission and the review of data should be revised to eliminate unnecessary or unimportant matters, reducing the workload of reviewing personnel. Expertise from the biomedical research community should supplement the scientific resources within the FDA to

achieve both better quality and greater efficiency in the evaluation process.

Another area had been suggested as presenting possible opportunities for expediting the approval process: regulatory requirements following the approval of a drug. The Commission concluded that changes here would not at this time expedite the process significantly.

A. APPLICATION OF THE STANDARDS FOR DRUG APPROVAL

The standards for approval of an NDA are set forth in the Federal Food, Drug, and Cosmetic Act and include: 1) whether the NDA contains "adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling"; 2) whether "the results of such tests show that such drug is unsafe for use under such conditions or do not show that such drug is safe for use under such conditions"; and 3) whether the NDA contains "substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended or suggested in the proposed labeling . . . ." (21 U.S.C. § 505(d).) Taken together, these provisions essentially describe a risk-benefit judgment based on the data in the NDA and other information available to the FDA.

The FDA has described the drug approval decision in the following terms:

> Each of these decisions is made on the best scientific evaluation which our staff and our advisors can provide to assess the available information. The terms and conditions of such decisions are set out in general terms in the law, and expanded in our regulations. It is essential that the public understand, however, that all of the bases and considerations of our judgments and decisions cannot ever be specified in rigid rules ahead of time. Decisionmaking in this complex and difficult area is continually

> evolving, as new medical and scientific issues arise. This is, indeed, what makes our responsibilities so awesome.
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> [R]isk-benefit assessment in the last analysis is a refined and discriminative judgment, the most critical of our mixed scientific and regulatory responsibilities. It is not readily described in general terms nor is it readily dismissed as trivial. It is instead the ultimate basis of most, if not all, of our decisions.6/

Clearly, risk-benefit judgments will vary, depending on multiple factors. For example, drugs designed for minor, self-limiting ailments are subjected to different safety and effectiveness assessments from those designed for life-threatening or debilitating diseases. Another factor is the alternative therapies available to treat the disease for which the new drug is offered; the relevance to an NDA approval decision, however, of the drug's safety or efficacy relative to another drug or nondrug therapy is a matter of controversy.

Another point of controversy is the acceptability in support of NDA approval of clinical data derived from studies performed outside the United States.

The Effectiveness Standard

When Congress amended the drug laws in 1962 to add the effectiveness requirement, it intended to enable efficacious drugs to be released to the public when experts judged, on the basis of valid scientific studies, that the drug would have the effect it was

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6/ Statement by FDA Commissioner Alexander M. Schmidt, in Regulation of New Drug R&D by the Food and Drug Administration: Joint Hearings before the Subcommittee on Health of the Senate Committee on Labor and Public Welfare and the Subcommittee on Administrative Practice and Procedure of the Senate Judiciary Committee, 93d Cong., 2d Sess. 207-08, 1974.

purported to have. The statutory formula for effectiveness is stated in the "substantial evidence" definition (21 U.S.C. § 355(d)), as follows:

> evidence consisting of adequate and well-controlled investigations, including clinical investigations by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.

From the legislative history of the 1962 Drug Amendments, it is clear that Congress intended for drugs to be approved (1) when proper scientific studies conducted by qualified experts established efficacy, (2) when experts reviewing those studies could fairly and responsibly conclude that efficacy had been established, and (3) even when such opinions existed despite the opinions of other experts to the contrary. The report of the Senate Judiciary Committee, for example, that supported the 1962 legislation clearly describes how the effectiveness standard should be applied:

> When a drug has been adequately tested by qualified experts and has been found to have the effect claimed for it, this claim should be permitted even though there may be preponderant evidence to the contrary based upon equally reliable studies. There may also be a situation in which a new drug has been studied in a limited number of hospitals and clinics and its effectiveness established only to the satisfaction of a few investigators qualified to use it. There may be many physicians who would deny the effectiveness simply on the basis of a disbelief growing out of their past experience with other drugs

> or with the diseases involved. Again, the studies may show that the drug will help a substantial percentage of the patients in a given disease condition but will not be effective in other cases. What the committee intends is to permit the claim for this new drug to be made to the medical profession with a proper explanation of the basis on which it rests.
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> In such a delicate area of medicine, the committee wants to make sure that safe new drugs become available for use by the medical profession so long as they are supported as to effectiveness by a responsible body of opinion.7/

In implementing the statutory standard for effectiveness, the FDA has promulgated regulations defining the essentials of "adequate and well-controlled investigations" and has issued manuals and guidelines to its reviewers detailing review procedures. In addition, court decisions, agency precedents, and the beliefs of individual agency personnel have had significant influence in shaping the present system. The standards for determining drug effectiveness remain a major source of controversy in the federal drug approval process.

Over time, the new drug approval system has appeared to many to have evolved from one intended to place important weight on a global evaluation of clinical findings made by experts, into one where approval is largely determined on finding two individual studies that comply fully with agency-specified testing procedures. In other words, the review process seems to some observers to have become a two-step process in which the FDA first ascertains whether any clinical trials submitted by the drug's sponsor conform with the details of the agency's criteria for "adequate and well-controlled" studies, and then the FDA determines whether, from among those that passed the first step,

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7/ S. Rep. No. 1744, to accompany S. 1552, July 19, 1962.

at least two studies can be isolated that independently demonstrate effectiveness.

This perception of the system has led drug sponsors to conduct redundant studies in the hope of guaranteeing that two will be found, on review, to have complied with the agency's interpretation of an "adequate and well-controlled" study. The current process also appears to have reduced the role of expert medical judgment of the evidence, while increasing the importance of strict compliance with what the pharmaceutical industry frequently believes are mechanical requirements.

The Commission believes that the process can be improved, without any change in the statutory requirements regarding effectiveness, through a more comprehensive view of what is necessary to establish substantial evidence of effectiveness under the terms of the statute. Demonstrating efficacy, in the narrow sense of showing useful pharmacotherapeutic activity, is relatively easy with most compounds. Clinical trials that substantially comply with the parameters for adequate and well-controlled studies and show positive results suffice to establish this fact and are scientifically persuasive. Indeed, there may be situations in which only one trial should be sufficient to establish effectiveness. For example, the FDA recently approved the use of timolol for the prevention of cardiac reinfarction on the basis of a single, multiple-clinic controlled study. This practice should continue in appropriate situations.

The key difference between the pharmaceutical industry and the FDA in this area seems to center on the degree to which a study must fulfill the precise criteria for an adequate and well-controlled study as set out in FDA regulations, guidelines, and precedents and as understood by the individual reviewers assigned to an NDA. In fact, what constitutes "adequate and well-controlled" should vary depending on what is known about the drug and the disease or symptom in question. Moreover, no clinical study is flawless, either in design or in execution. From the FDA's perspective, the agency is only conducting a sound scientific analysis of the research presented. Yet, in the view of some drug sponsors, FDA reviewers tend to focus on insubstantial deviations from technical requirements without considering whether, despite the deficiencies, the study provides reliable scientific evidence of the drug's

effectiveness. It seems to be a widespread impression in the pharmaceutical industry that NDAs are being judged on the basis of their fulfillment of inflexible, preconceived criteria regarding study design and conduct, rather than on a reasonable assessment of the results of the study.

This approach to NDA review might be contrasted with that which occurred with the drug propranolol for the treatment of angina pectoris. Evaluating over 30 studies, an FDA advisory committee concluded that none of the criteria for an adequate and well-controlled study were met in all particulars by any one study. Nevertheless, on the basis that the accumulation of all the data amounted to substantial evidence of effectiveness for propranolol in angina, the committee recommended that the drug be approved as effective. The Director of the Bureau of Drugs agreed with the advisory committee's conclusion and approved the angina claim on the basis of his evaluation of all the evidence before the agency. In addition, the Bureau Director -- who was a former clinical pharmacologist specializing in cardiology -- found that a substantial number of the studies substantially complied with the requirements for an adequate and well-controlled study and showed a consistent pattern of drug efficacy.

To the Commission, both the committee's advice and the FDA's acceptance of it, based upon the totality of scientific evidence, appears fully consistent with the intent of Congress and is much more in accord with good science and sound public policy. Regrettably, the FDA was severely critized for that decision, not because of any dispute over the efficacy of propranolol for angina, but because of the doubts that the technical requirements for an adequate and well-controlled study had been met and the disagreements in the propranolol on that narrow point.

In order to avoid such criticism in the future and institutionalize this rational approach to the evaluation of scientific evidence, the Commision believes that the FDA should incorporate it in a regulation. In particular, where no two NDA studies can be isolated that fully comply with the criteria for being adequate and well-controlled, consideration should be given to the degree to which all studies substantially fulfill these criteria. Those which can provide reliable scientific information should be assessed together,

so that, where proper, the strengths of some may be used to compensate for the weaknesses in others. If the accumulation of data so demonstrates, the drug should be found to be effective within the requirements of the law.

The role of the cardiologist/clinical pharmacologist in the propranolol case also emphasizes the importance of expert judgment in the evaluation of controlled trials. The statute not only permits experts to review the evidence in support of a drug's efficacy; it demands the involvement of experts. The observations of experienced clinical investigators are quite relevant in determining whether a study is adequate and well-controlled, what its results show, and how these results should be interpreted in light of the entirety of scientific information on a drug. Therefore, the Commission recommends that the FDA revise its procedures to ensure that a range of experts -- from inside and outside the FDA -- consider the body of evidence and advise whether it can be concluded "fairly and responsibly" that the drug will have the effect that is claimed for it. Experts, including clinical investigators and specialists in health care, should be directed to examine all relevant evidence and to make their assessments of efficacy based on the totality of evidence.

This emphasis on expert judgment in no way removes from the Secretary of Health and Human Services and from the FDA Commissioner the ultimate responsibility for approval of a new drug. Rather, it stresses the basis on which such final decisions should be made.

- The FDA Commissioner should clarify through regulation the interpretation and application of the statutory and regulatory standards for establishing substantial evidence of the effectiveness of a new drug. Effectiveness should be found to have been demonstrated either by two -- or when appropriate, one -- adequately designed and well-controlled studies that individually provide the necessary substantial evidence of effectiveness or by the accumulation of data from adequately designed and well-controlled studies that taken together provide such substantial evidence.

- The FDA Commissioner should revise the FDA's review procedures, consistent with the Congressional intent, to ensure that due weight be given in the new drug approval process to the judgment of experts, including clinical investigators and medical specialists, as to whether the effectiveness standard has been met.

Relative Safety and Efficacy

The question of whether NDA decisions should include an assessment of the drug's safety or efficacy relative to other available therapies has frequently been debated. At first blush, the argument that the FDA, in making the overall risk-benefit assessment for NDA approval, should consider a drug's relative efficacy or safety has some appeal. Certainly, if it can be shown that two drugs have identical side effects but one has a distinct advantage in efficacy (such as a better absorption rate, a longer duration of action, or superior performance in individual patients), it is difficult to understand why approval of the "less effective" drug should be mandated under law. Similarly, the less safe of two comparably effective agents might arguably also be kept off the market.

The trouble is that scientific judgments regarding relative safety and efficacy are very difficult and prone to error. Evaluation procedures tend to develop information on "group" or "mean" drug performance, rather than on the responses of individuals to a given drug. What may be less effective (or less safe) in one group of patients -- even in the majority of patients -- may be more effective (or more safe) in certain other individuals who are seeking treatment. Thus, individual physicians making treatment judgments for individual patients are generally in the best position to determine which alternative therapy has the most favorable risk-benefit ratio in each case. For these reasons, the approval of a drug that is less safe or effective than others already available may nevertheless be justified when evidence exists of a subpopulation of patients who will benefit specifically from the drug and when the agent's role in therapeutics can be properly stated in labeling.

In the real world, of course, no two drugs have identical actions, either therapeutic or adverse. Each presents special advantages and disadvantages, many

of which cannot be identified in preapproval trials. If relative efficacy or safety were used to keep a new drug from entering the marketplace, the FDA would be precluding greater clinical experience and the refinement of the drug's risk-benefit ratio.

For these reasons, Congress has not given the FDA the power to consider relative efficacy in making NDA decisions. The legislative history of the Drug Amendments of 1962 clearly provides that NDA approval should be based on considerations of efficacy with respect to the entity under review and should not be influenced by comparisons with other available drugs or therapies.

Although relative safety is part of the NDA risk-benefit assessment, the FDA has rarely denied approval to a drug on this basis. Where it has occurred, the drug involved has generally been found to offer very few benefits when compared to other therapies, while at the same time it was significantly more toxic both in comparison to other therapies for the same condition and in comparison to high-risk drugs approved for other uses. In other words, the drug was held to exceed the level of risk accepted by society for drugs generally.

- Drugs should generally be considered for approval on the basis of judgments regarding the safety and effectiveness of the drug per se. Only in unusual cases should relative safety enter into approval decisions.

The Use of Foreign Data in Evaluating Safety and Effectiveness

There is no statutory guidance on the degree to which the FDA should rely on safety and effectiveness data derived from studies conducted outside the United States in approving an NDA. The FDA policy has evolved over time. Originally, the agency required all critical studies to be conducted in this country. Since 1975, the FDA has shown far greater willingness to accept foreign data. Nevertheless, confusion still exists within the pharmaceutical industry as to the type of foreign trials which are acceptable in support of an NDA and whether approval can be based solely on foreign data.

Present FDA policy (21 C.F.R. § 312.20) permits the "appropriate" use of data from studies performed abroad and conducted in accordance with certain internationally accepted ethical standards and other scientific requirements. In elaborating on that language, the FDA regulation does not require that Phase I and Phase II studies be duplicated in the United States but contemplates for Phase III the acquisition of data obtained from randomized controlled clinical development studies conducted here. The data need not necessarily be confirmatory but may serve to provide information not found in the foreign studies. Agency regulations currently permit one exception to this restriction: For a drug developed to treat a disease that is rare in the United States, the approval requirements can be met by foreign clinical data alone.

Past objections to total reliance on foreign data, such as a lack of confidence in the quality or integrity of foreign trials and problems of investigating raw data overseas, have become increasingly invalid as many countries have now proved fully capable of conducting meritorious clinical trials and producing reliable, analyzable data. Multinational companies have good reason to ensure that clinical trials, wherever done, can be used effectively to gain approval from the most demanding regulatory agencies. The United States is clearly a major commercial target for such firms.

The justifications now offered for requiring at least some American data for the approval of drugs here are as follows: There are varying levels of resistance to disease in different parts of the world, such as the resistance of bacteria to anti-infective agents; diagnostic criteria and therapeutic practices may differ; and, most importantly in the view of the FDA, there should be some United States experience with the drug before making it widely available in this country. It is often stated that United States marketing involves the largest single exposure of a drug to a particular population and that for both scientific and sociopolitical reasons, there ought to be some domestic experience with the drug.

These considerations deserve attention, but they do not automatically demand the repetition of clinical trials. For example, the fact that the resistance of bacteria to anti-infectious agents may

differ in various parts of the world is no less true than the fact that resistance varies in different parts of this country or even from one hospital to another in the same city. Diagnostic criteria (and therapeutic practices) may indeed differ in various parts of the world, but international standards have reached the point where this, too, is not a powerful reason for demanding the repetition of well-done foreign studies.

Arguments about sociopolitical needs for domestic research frequently appear to suggest that the American public will be saved from drugs in which toxicity only appears after widespread use or use over a considerable period of time. In fact, such suggestions have little relevance to questions concerning the use of foreign data. Although delays in NDA approval caused by replicating foreign studies may buy time for toxicity to appear abroad, and thus may or may not be socially desirable, they should not be confused with the purposeful accumulation of "better" data.

It is thus inappropriate to have a standard policy of always requiring one or more randomized controlled clinical trials to be performed in the United States. The Commission believes that unless foreign clinical trials have been performed in populations with different ethnic and genetic composition or different clinical practices, so as to suggest danger in extrapolating safety or effectiveness findings to the American population, it is not necessary to repeat randomized controlled clinical development trials in the United States. Nevertheless, it also seems unwise to approve a drug for this market without some native experience. The Commission believes, however, that such experience can be obtained from noncontrolled trials, wherein clinical experts here use a new drug for patients with the disease or symptoms in question, according to the data acquired abroad, to see whether the results regarding safety and efficacy in the United States are substantially similar to those observed abroad.

- Data on drug efficacy and safety derived from studies conducted in other countries should be given full weight as evidence in proportion to their quality. The routine replication of randomized controlled trials should not be required; rather, when relevant foreign

trials are convincing in themselves, it should be sufficient for a sponsor to provide clinical experience in the United States to supplement the results observed abroad.

B. THE NDA SUBMISSION AND ITS REVIEW

The NDA process really begins when a sponsor judges that sufficient data have been collected on a new drug, based on advisory information from the New Drug Application form, FDA guidelines, and any conferences held with the FDA during the drug's development. At that point, the sponsor compiles and submits an NDA. The submission and review process has been described by the FDA as follows:

> It is hoped that, by the last [conference held during the IND process], the FDA and the sponsor of the IND will be in basic agreement about the kinds and adequacy of data on which the NDA will be based, so that the NDA will be simply a formal pulling together and organization of data acquired through many kinds of trials conducted over several years of drug development.
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> One of our goals is that most scientific problems of safety and effectiveness will have been elucidated in the IND phases so that drugs which could never pass the NDA tests on safety and effectiveness are not even submitted in NDA form. Thus, NDA review becomes simplified to a final review of all pertinent data and a summary of the rationale and justification for the decision to be taken. For those reasons, we must recognize the fact that most new chemical entities for which an NDA is submitted are eventually approved for one or more indications. This last point is essential to understanding the real issues in the drug review process and the critical points at which those issues are resolved.

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The NDA must contain all information, both favorable and unfavorable, which the sponsor has obtained through investigations relating to both the safety and the effectiveness of the new drug. Each NDA consists of about 2 to 15 volumes of summary material accompanied by about 10 to 100 volumes (occasionally up to 400 volumes) of raw data.

By law, the FDA has 180 days in which to review the NDA and either approve or disapprove the application. The FDA may withhold final action on the NDA pending the compilation and submission of additional data, however, if the applicant agrees to the extension.

The grounds for refusing to approve an application are specified in the Act and regulations. Where the FDA proposes to refuse to approve the NDA, the applicant is notified of an opportunity for a hearing on the question of whether the NDA is approvable.

[The FDA expects] the IND to anticipate and prevent submission of an NDA which would demand absolute disapproval. More frequently, an NDA is submitted, deficiencies are discovered, and the applicant notified by means of a letter of nonapproval or through a conference with the Agency. At this stage the applicant will commonly take steps to remedy the deficiencies noted, a revised NDA is submitted, and a new review is made by the drug review team. After one or more such recyclings, all deficiencies are generally corrected and the NDA in its final amended form may then be considered approvable. At that point, a conference is arranged to discuss the final printed labeling

which will contain the precise conditions under which the drug may be used. Once the indications, warnings, and other matters in the labeling are agreed upon, the NDA is approved and marketing may commence.

In this process, those NDAs with deficiencies too serious or too great to be remedied will either be withdrawn by the manufacturer or disapproved outright by the Agency. But more commonly the letters of disapproval constitute a problem identification step, which permits the manufacturer to reassess his submission and revise it in accord with FDA requirements.

The input on the recommendations on whether to approve or disapprove an NDA comes from the FDA drug review team. A consultant may be utilized in this process. The team's recommendation is discussed with the group leader and the Division Director, either of whom may disagree with any of the recommendations. Reasons for approval or disapproval by the supervisors are noted in the record. The NDA is then forwarded to the Director of the Office of Scientific Evaluation [now the Office of New Drug Evaluation], accompanied by a draft letter to the firm which reflects the views of the Division Director. It should again be noted that in most cases there is agreement between reviewers and supervisors in the Division.8/

8/ Statement by FDA Commissioner Alexander M. Schmidt, In Regulation of New Drug R&D by the Food and Drug Administration: Joint Hearings before the Subcommittee on Health of the Senate Committee on Labor and Public Welfare and the Subcommittee on Administrative Practice and Procedure of the Senate Judiciary Committee, 93d Cong., 2d Sess. 209-10, 1974.

An NDA is normally reviewed by personnel from three different branches of the Bureau of Drugs: physicians, pharmacologists, and chemists associated with the reviewing divisions in the Office of New Drug Evaluation; statisticians from the Division of Biometrics in the Office of Biometrics and Epidemiology; and specialists in biopharmaceutics from the Division of Biopharmaceutics in the Office of Drug Monographs. Each NDA is assigned to one of six reviewing divisions within the Office of New Drug Evaluation, specializing in particular areas of therapeutics, for review and control. Within each division, medical officers are assigned to specific NDAs on the basis of their expertise, and a senior medical officer normally serves as the leader of the review team for a particular NDA.

Work priorities for team members are set in various ways, which are not always coordinated with one another. Each team member has his or her own workloads, priorities, and assignments from immediate supervisors. Team leaders must deal with members from both their own divisions and elsewhere in the Bureau of Drugs. The FDA has applied a classification system, based on a drug's perceived therapeutic potential, to set relative priorities among the NDAs undergoing concurrent review.

Broadly stated, the principal purposes of the staff review are to determine whether (1) the studies conducted with the subject drug were properly designed, conducted, and analyzed in accord with the applicable requirements, (2) the data from those studies support the conclusions represented, (3) the conclusions about the drug are properly described in the proposed labeling, and (4) the procedures for the drug's manufacture and control will ensure its consistent purity, potency, and bioavailability.

The complexity of the process by which these determinations are made can be illustrated by the decision-making steps regarding the effectiveness of the drug: The clinical studies considered pivotal are first scrutinized to determine compliance with the criteria for being adequate and well controlled. They then are subjected to a lengthy process of statistical validation, dissection, and reanalysis. The medical officers and biostatisticians reanalyze this mountain of data, often setting aside the analyses and summaries presented in the NDA, in order to make their own findings from the clinical investigations.

While this evaluation is proceeding, the FDA is verifying the reliability of the data. As part of the NDA, the sponsor is required to submit the individual case records for each patient in whom the drug has been studied. A typical new chemical entity NDA may consist of hundreds of volumes, with most of the bulk attributable to the case-report forms. In the course of its review, field inspectors visit the offices of clinical investigators and the laboratories of the sponsors to examine the records containing the raw data. These inspections are done routinely, not done just for cause, with all NDAs concerning new chemical entities.

Once the medical officers and biostatisticians are satisfied that at least two pivotal clinical studies are unflawed from a regulatory perspective and offer positive results, the NDA may be referred to an expert advisory committee for its recommendation.

When the FDA is satisfied that a new drug is effective and otherwise approvable, the reasoning behind the decision is extensively documented in the Summary Basis for Approval, which becomes publicly available under the Freedom of Information Act once the drug is approved. The length to which the FDA goes in preparing the Summary Basis of Approval exceeds any legal requirement imposed on the agency and is unlike the practice of regulatory agencies in other countries. More importantly, the documentation process contributes, in some cases, to a delay in final approval of a drug.

Format and Content of NDA Submissions

The overriding objective of the NDA review process is to determine as efficiently as possible whether a new drug has been shown to be safe and effective and can be manufactured with consistent quality and purity. This goal can be furthered by reorganizing the format of the NDA and streamlining its contents.

Because the sponsor is now required to include all the raw clinical data in the form of individual case records, NDA submissions contain so much information that they present both severe handling problems and the potential for unnecessary review and analysis by medical officers and statisticians. The Commission does not believe that NDAs should have to be of such proportion. In the United Kingdom, whose Committee

on Safety of Medicines consistently maintains a less time-consuming but high-quality drug approval process, a request for marketing approval requires a submission containing only several volumes summarizing clinical data on the drug. This summary document, called a CSM-2, has been found to serve well as the basis for efficient and thorough review by both regulatory staff and outside experts and offers an excellent model of what our NDA submissions might better be like. Most drug regulatory authorities in other countries also require submissions consisting of thoughtfully drawn summaries; only one other nation (Canada) requires the routine submission of individual case-report forms (though that country's approval times are generally shorter than the United States').

It is the Commission's opinion that had Congress intended NDAs to encompass the level of detail now contained in them, it is unlikely that Congress would also have required their review to be completed in 180 days. Accordingly, the Commission recommends that the requirement for the routine submission of individual case-report forms be eliminated and that an adequate summary of clinical information be submitted instead by the NDA sponsor. Case-report forms should continue to be required when serious adverse reactions or deaths have occurred or when the special nature of a study makes their ready availability purposeful. In all other instances, they should be supplied to the FDA on request but be retained by the sponsor, even after NDA approval. The FDA has preliminarily indicated its intention to eliminate the requirement for the routine submission of all individual case records, and the Commission applauds this step.

There remains, however, the issue of defining the "adequate summary of clinical information" that will be helpful to the FDA. Unfortunately, there may be no single definition of an adequate summary that would apply in every case. The review team, its consultants, and ultimately the FDA and the public, must unquestionably be satisfied as to the validity of the data and the conclusions from the determinative studies contained in an NDA. The Commission believes that before the NDA is prepared one or more conferences should occur between the sponsor and the FDA (including any outside experts who are advising the agency regarding the drug) to discuss which kinds of data in the NDA should be summarized in greater or lesser detail and

how those data should be presented and analyzed. Furthermore, the earlier and more significant involvement of outside experts in the review process (recommended later in this report) should go a long way toward helping avoid excessive or inappropriate staff review of clinical data. The Commission would discourage, however, the establishment of any requirement that would, in effect, expect the sponsor to provide tabulations that indiscriminately include every bit of data from the case report forms. Replacing case-report forms merely with extensive tabulations would help with the physical size of the NDA but would be counterproductive to the true purpose of the review process as envisioned by the Commission.

As stated above, full information on all serious adverse reactions would still be contained in the NDA. Currently, this information is presented in an NDA twice. One is on the Drug Experience Report on FDA Form FD-1639. This form, set up for coding to permit entry of the data into a computer, was conceived to be used by physicians to report drug reactions on marketed products. Pharmaceutical companies, however, must also use the form to submit in the NDA information on drug reactions occurring during the IND process; several volumes in an NDA consist of these forms. All of the information they contain is also presented elsewhere in the NDA in more readily reviewable form, and all adverse reactions are summarized in tabular form and analyzed in several different ways both for each study and for the NDA as a whole. Particularly serious or complex reactions are each reviewed in detail in the study summaries. Thus, the Form FD-1639 appears to serve no useful purpose in the NDA. The Commission recommends the elimination of these forms from the NDA.

The Commission recommends that NDA submissions consist of separate sections tailored to fit into the FDA's current functional units, as follows: 1) the volumes for the FDA discussion, containing drug chemistry, synthesis, manufacturing, and quality control procedures; 2) the volumes for pharmacology review, containing data on pharmacology, toxicology, pathology, teratology and similar matters derived from animal studies; 3) the volumes for biopharmaceutics review, including information on drug metabolism; and 4) the volumes for medical and biostatistical review containing data from clinical efficacy and safety studies. The total number of volumes would depend primarily on the

drug type, the number and types of animal and clinical studies done, and the complexity of the information being presented. Each reviewer should be supplied copies of the volumes needed for his or her work. This format would simplify paper handling integration of amendments and supplements and review activities. It would also enable parallel review of each segment, as recommended below.

In addition to the volumes just described, the NDA should also contain both draft labeling and a draft Summary Basis for Approval for the drug. Currently, the Summary Basis for Approval is prepared after the drug has been found to be approvable. Although this documentation may be prepared by either the FDA or the sponsor, it is usually done by the medical officer; the time-consuming nature of the task often can delay final approval. Therefore, the Commission recommends that a draft of the Summary Basis for Approval be prepared by the sponsor, in the format preferred by the FDA, and submitted with the NDA. It would state the case, as the sponsor's scientists and expert consultants see it, for approval of the drug and would be annotated for easy reference to the relevant evidence contained in the data summaries. The FDA, of course, would review and revise that draft as necessary, but considerable time would be saved. The draft labeling would continue to be submitted by the sponsor, as at present. It would also be annotated for easy cross reference to both the Summary Basis for Approval and the data summaries.

- NDA submissions should be greatly streamlined. Summary presentations of data should replace the individual case-report forms. The clinical sections of NDA submissions should be designed to facilitate efficient review and should contain tabulations of all the data needed to assess the design, conduct, and analysis of the important studies; they should not routinely include the individual case-report forms or tabulations of every datum they contain.

- To enable parallel review by the different disciplines in the FDA, NDA submissions should consist of separate sections covering chemistry, pharmacology, biopharmaceutics, and clinical studies on the drug. In addition, the NDA should contain a draft Summary Basis of Approval for use by the FDA.

The Review Process

Reducing the volume and improving the format of the NDA submission is only a partial solution. It is equally important to streamline the review process once the NDA has been filed.

The procedures used for reviewing applications for medical devices in the FDA's Bureau of Medical Devices offer a good model. If it were applied to drug review, the NDA approval process would function as follows: Immediately on receipt, the FDA would promptly conduct an initial review of the application and discuss with the sponsor any potential deficiencies preventing an evaluation of the NDA. If the FDA determined that the application is not seriously deficient, or once the deficiencies have been remedied, review by the different disciplines in parallel should begin immediately. That is, the medical officer and biostatistician would both commence their reviews of the clinical data, while the chemist, biopharmacist, and pharmacologist were each carrying out their reviews. As questions or issues arise during staff review, they should be communicated to the sponsor by the individual reviewer, as directly and informally as possible. If, as recommended below, the development of this drug in the IND phase involved outside experts as well as the FDA (on the request of the FDA or the drug sponsor), the summary of clinical studies would be referred at the same time to the outside experts. Review should be straightforward, since the FDA and any outside experts would already have become familiar with the drug, potential problems should have been identified and worked out in the conferences during clinical development studies, and the need for a highly intense level of FDA review would be decreased.

As the Bureau of Drugs is currently organized, the overall management of review teams handling multiple NDAs is inherently difficult. Described earlier were the components to which members of the review team are assigned. Coordination among these components, as well as among different NDAs, requires close and skillful coordination of personnel. Although valid reasons may exist for retaining the current organization by professional discipline, this point should be reconsidered. If the present lines of organization are kept, however, some attention must be paid to managing project-team operations.

The Commission believes that the challenge would be better met if one or more senior managers at the bureau level were assigned solely to oversee operations, rather than also having policy and planning responsibilities. In addition, the now well-developed techniques for managing organizations that operate in the project-team mode should be more extensively applied. The conflicts that arise involving priorities set by different project teams of which the same person is a member have to be resolved among the appropriate managers. Project-team leaders and division heads must have a more direct role in the setting of goals and priorities for those team members not directly under their supervision.

Within the drug review process, priorities will have to be established if resources are from time to time inadequate or if conflicts arise in scheduling individual workloads. These situations should be kept to a minimum, however, if the other recommendations of this Commission are followed. Indeed, expediting the drug approval process should apply to all drugs, not those few each year that are uniquely important. Accordingly, the current FDA practice of classifying all drugs into categories based on a standard related to therapeutic gain should become unnecessary. Moreover, as a general rule, the overall drug approval process should not assign priorities or mandate preferential treatment for particular drugs. The Commission is concerned that, under FDA's current system, classifications are made so early in the development process that they may lack scientific basis and sometimes lead to unjustified discrimination in the handling of NDAs. Normally, NDAs should be processed on a first-come, first-served basis. Of course, in extraordinary situations, such as for a life-saving drug needed by large numbers of people, the public health requires special, fast-track handling of the NDA.

Other elements in the current review procedure present important obstacles to timely decision making. For one thing, NDA review is sometimes delayed when portions of data are rereviewed some months or even years later, such as in the case of personnel turnover or in the case of toxicology studies that were submitted and reviewed during the IND process. Certainly, new information or other reasons make reconsideration of the data necessary in some cases, but every effort should be made to eliminate any unwarranted rereview.

Documentation of the FDA's internal reviews and decisions, as well as correspondence with drug sponsors, also appears to increase the agency's workload and slow drug approvals. For example, the long delays now seen between favorable advisory committee recommendations and final approval are worrisome and appear in no way useful to the public health. The Commission believes that recommendations such as introducing more informal communications between the FDA and a drug sponsor, and having the sponsor provide a draft Summary Basis of Approval, will help alleviate the problem, but the FDA Commissioner should take further steps to control the level of documentation of NDA decision making and ensure that documentation requirements do not interfere with timely action on NDA approvals.

- Management of NDA review responsibilities should no longer be split among separate offices of the Bureau of Drugs. Each professional member of an NDA review team should be responsible to a single team leader with regard to productivity goals on that NDA.

Requirements Regarding Chemistry, Manufacturing Controls, and Biopharmaceutics

Difficulties in satisfying NDA requirements concerning chemistry and manufacturing controls have significantly contributed to delays in the approval of new drugs. The 1980 GAO report cited earlier concluded that the FDA's review of the chemistry portion of the NDA takes longer than do the pharmacological and medical reviews. Subsequently, the FDA reported that the majority of the deficiencies in NDAs are related to chemistry and manufacturing. Areas of deficiency cited most frequently by the FDA, according to a study done by the FDA Office of Planning and Evaluation, were analytical procedures, stability testing, container specifications, and precautions ensuring the purity of raw materials.

Although issues over chemistry requirements do indeed arise with great frequency in the review of NDAs dealing with new chemical entities, the Commission believes that their significance to the public health is rarely of the same magnitude as the kinds of issues regarding clinical evidence of safety and effectiveness

discussed elsewhere in this report. The chemistry problems stem from a different set of reasons; they often appear overly technical and trivial; and their avoidance or resolution calls for a special approach.

The present NDA requirements for information about chemistry and manufacturing controls may be excessive. Many of them are adequately encompassed within the FDA Good Manufacturing Practice (GMP) program and do not warrant duplication. Beyond that, data requirements should be strictly limited to what is importantly relevant to drug safety, efficacy, and purity. The Commission recommends that the FDA, in collaboration with industry and academic experts, undertake a complete analysis of the chemistry and manufacturing controls requirements in the NDA process. This analysis should begin by defining the essential purposes of NDA review of those matters, as opposed to reliance on GMP requirements. Standards that are sound, not only from a chemist's viewpoint but also from the perspective of other disciplines, such as clinical pharmacology, should be developed specifying the chemistry and manufacturing information that the FDA must have in an NDA, to ensure the safety, efficacy, and consistent quality of a new drug.

The FDA's approach to managing the chemistry review within the NDA process also needs to be addressed. The present managerial structure in the Bureau of Drugs is not well suited to the task of monitoring the chemistry review process. The senior line managers usually have backgrounds in medicine or biology and may not fully understand chemistry problems. As a result, requests by chemists for more information, additional specifications, or special analyses cannot routinely be reviewed by these managers for reasonableness or justification. The role of supervisory chemists within the reviewing divisions should include this responsibility, as long as the interchange with the NDA sponsor is not delayed unduly. In that regard, communications between FDA and industry chemists should be timely and informal, where appropriate, in order to avoid minor chemistry issues appearing in deficiency letters, many of which could probably be cleared up readily with a telephone call.

Similarly, the biopharmaceutics requirements for NDA approval should be examined. This relatively new discipline has evolved quickly and appears to be

playing an ever-increasing role in NDA approvals. Since all clinical bioavailability studies are time-consuming and costly in their utilization of scarce, sophisticated and valuable testing resources, it is important that NDA requirements demand only that information necessary to establish drug quality, safety, and efficacy. The review of additional, nonessential information burdens FDA personnel and delays the review process.

- The FDA, in collaboration with industry and academic experts, should undertake a fundamental analysis of those portions of the NDA review process that have to do with chemistry, manufacturing controls, and biopharmaceutics, in order to delineate more clearly the information essential for review, revise the requirements accordingly, and establish better managerial oversight of these portions of the review process.

C. UTILIZATION OF OUTSIDE EXPERT ADVICE

The FDA currently utilizes outside experts in the NDA review process. Fifteen separate prescription drug advisory committees, corresponding to therapeutic drug groups, advise the six reviewing divisions of the Office of New Drug Evaluation of the Bureau of Drugs. While the existing advisory committee system serves a useful purpose, a greater use of independent expert review can ensure both a high-quality drug supply and the prompt availability of useful new drugs. Government and academic medical experts in this country represent a valuable national resource capable of making a much greater contribution to the drug regulatory system than they are currently invited to do.

A broader role for these experts requires that they be involved earlier and more continuously with the drug. At present, advisory committees are rarely consulted with regard to an NDA before it has been under staff review for an extended period. Committee review late in the process lengthens the overall review time and can result in considerable delay if the committee finds new questions or problems. The Commission recommends, therefore, that the FDA undertake several initiatives and policy changes to enable more timely and substantial involvement of outside experts in the drug review process when such interaction would be helpful.

First, the NDA process should be modified so that outside experts could, on the request of the drug sponsor or the FDA, become involved with each new chemical entity (except perhaps for later members of a series of related drugs such as benzodiazepines or nonsteroidal anti-inflammatories) and each important new use of an approved drug. Specifically, the Commission recommends that the FDA develop a register of a large number of outside professionals with high status in the area of their particular expertise who are willing to assist the agency. When the FDA is advised that a new drug is about to enter full development (commonly, when clinical development trials are to begin), and when the sponsor or the FDA believes that involvement of outside experts would be helpful, the FDA would designate an expert consultant, or a panel of three experts, from the register to participate in the further IND and NDA processes involving that drug. In the case of a drug not primarily being developed in the United States, the outside experts would be designated as soon as feasible. The consultant or members of the panel should be available to serve until the NDA has been approved, disapproved, or withdrawn.

This recommendation would not affect the current advisory committee structure, which would continue as is. Rather, the outside experts would extend the capabilities of and serve advisory committees. For any particular drug, current advisory committee members may serve as the consultant or on the panel, but in some areas of therapeutics with heavy workloads, most panel members or consultants would be chosen from beyond the particular advisory committee itself. From time to time, of course, the number of drugs concurrently under development in certain areas of therapeutics may make it impractical to have a separate consultant or panel of three consultants involved with each NDA, even though desired by the FDA or the sponsor. Under those circumstances, the FDA should allocate its consultant resources in whatever pragmatic fashion best ensures that each application receives due consideration and equitable treatment.

Timing and Scope of Involvement

In the ordinary circumstance when the drug is primarily under development in the United States, expert involvement would begin with participation in the pre-clinical-development-studies conference, at which the

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sponsor's development plan is discussed. Thereafter, the consultant or panel would participate in FDA reviews of new IND projects, evaluation of periodic reports and any serious adverse reaction problems, and most further conferences between the FDA and the sponsor. Prior to filing of an NDA, the outside experts would assist in the development of specific plans of data summaries and analyses to be presented in the NDA.

Immediately on submission of the NDA, the clinical data summary would be promptly transmitted to the outside experts. Because of being involved during the IND phase, the experts should readily recognize those areas of the NDA that require special scrutiny. The consultant or panel of experts would then participate in the presentation of the NDA to the appropriate advisory committee. The advisory committee, in turn, would advise the FDA on the approvability of the drug; this formal recommendation to the FDA would be voted on in public session, as at present. The final decision whether to approve an NDA would, of course, remain the responsibility of the FDA.

There is a sound basis for expecting that broader use of expert consultants would improve the efficiency and quality of the NDA process. In the proposed system, both sponsor and regulator can confidently anticipate that their work will undergo timely peer review. The FDA has asserted that defective submissions are often a reason for the slowness of new drug approval process. Industry complains of excessive demands for data, idiosyncratic reviewer behavior, and unwarranted delays. The greater involvement of the scientific community in the development of the drug, plus the earlier initiation of outside expert review, would reduce the likelihood of such occurrences. Company scientists would have a powerful additional incentive to see that their submissions are impeccable. If the review process is to be completed in six months instead of two years, the sponsor would have to avoid mistakes and avoid filing significant amounts of supplementary material. Professional and company reputations would be at stake. Correspondingly, the FDA would find itself under substantial pressure to perform constructively. Professional pride would give FDA reviewers additional incentive to reflect carefully on the relevance and significance of their critiques and recommendations.

Beginning the involvement of outside experts during the development of the drug should tend to reduce unnecessary arguments at the time of NDA review over how the study should have been designed. By virtue of their involvement with the design and execution of the development plan, the experts should be eminently qualified to serve as reviewers of the results of the studies, as well as consultants to the FDA. Thus, NDA review should go significantly faster, both because problems should have been avoided and because review by the FDA and the advisers will be concurrent rather than sequential. At the same time, it should serve to buffer the FDA against unwarranted criticism of its decisions, allow a substantial reduction of paper flow, and go a long way toward improving the efficiency and objectivity of the entire approval process.

- The system of new drug development and approval should be modified to afford a more significant role to experts from outside the FDA, drawn from the academic and government biomedical research communities. On the request of the FDA or the drug sponsor, outside expert consultants should be available both to advise in the investigational development of each new chemical entity or important new use of an approved drug and to participate in the review of its NDA.

Obtaining Outside Expert Participation

Additional advisory resources will be needed to implement this recommendation, at least in certain areas of therapeutics, and it is imperative that the FDA seek for this purpose the participation of the best qualified outside experts available. To do so, several obstacles need to be addressed. Many leading authorities on therapeutics and research whose advice could be useful to the FDA do not currently serve in any advisory capacity. Various reasons have been cited for the FDA's inability always to have access to the best advice available, including (1) stringent conflict-of-interest regulations that make it very difficult for those who do clinical research with new drugs -- and thus those who know the most about them -- to serve on FDA advisory committees; (2) budgetary constraints that prevent the government from seeking more extensive involvement by outside experts; and (3) the fact that professionals are often hard pressed to spare the time to perform

public service, especially when its significance does not appear to be great.

The problem of motivation is easily resolved, since the greater involvement of outside experts in the review process should significantly enhance their willingness to participate.

Concerning budgetary constraints, the Commission believes that the FDA may be able to fund a larger advisory resource without seeking additional budgetary authorization because of the resource allocations possible as a result of several of the recommendations in this report; some of these gains could be applied to obtaining additional outside expert advice. If necessary, the Commission recommends that the FDA pursue funding alternatives. For example, it might be possible to impose a fee on the sponsor of each NDA that is to be reviewed by outside consultants, the monies so obtained to be earmarked solely for compensating outside experts and reimbursing their travel expenses. As another possibility, the FDA might contract with appropriate professional bodies to provide broadly based expert advice; part of the cost of this service, however, might be paid directly by the NDA sponsor. This combined funding approach has been done in the past, for example, by the Bureau of Foods in connection with its review of the safety of food additives. Such an approach would ensure the continuing availability of an adequate outside expert resource if, as has happened in the past, the Executive Branch chooses for budgetary reasons to freeze or cut back on agency employment.

The conflict-of-interest issue is dealt with more fully in a separate recommendation. Adoption of the above recommendation should also help alleviate the problem. The outside experts would not necessarily be voting members of advisory committees, and since they would serve at any given time only in connection with the review of a specific drug or group of drugs, the likelihood of their having significant conflict-of-interest problems would be appreciably diminished.

To gain the services of the best qualified experts in various fields of therapeutics, the FDA should seek the assistance of professional societies, universities, government agencies, and other appropriate bodies, communicating to these groups the intention of enlarging the role of the scientific community in

the new drug approval system in order to improve its efficiency. Professional societies and others should be asked to encourage the participation of highly qualified individuals and to recommend or designate experts who would be willing to serve on the agency's consultant panels.

The FDA and drug sponsors should also encourage the practice of having outside experts who investigate a drug present their views of it to FDA personnel and consultants at appropriate meetings.

- The FDA Commissioner should seek the assistance of leading professional societies, universities, and other appropriate bodies in an effort to gain for the FDA the services of consultants who are among the most qualified experts in various fields of pharmacology and therapeutics.

D. POSTAPPROVAL REGULATION OF DRUGS

Postmarketing surveillance and postapproval studies can provide valuable information concerning uncommon or unanticipated side effects, new indications for use, and dosage for special types of patients such as children and the elderly. Important distinctions must be drawn between and within the types of postapproval research, however, in order to assess the degree to which the availability of one type or another may either expedite drug approval or lead to the earlier discovery of side effects not detected in the IND phase. The Commission's mandates limited consideration of postapproval research to achieving these two objectives, and thus other potentially important uses of postapproval surveillance and studies are not discussed.

Postmarketing Surveillance

Drug surveillance refers to the observation of persons who may use drugs, for the purpose of detecting unexpected effects, beneficial or adverse, from the drugs. Historically, there have been many kinds of postmarketing surveillance, which fall into two general categories. One, in place for a long time, consists of a network of activities that operate independently of a drug sponsor and generally are not oriented to monitoring specific drugs. Instead, this surveillance begins with observed events -- patient

injury or unanticipated patient benefit -- and looks back to seek an association with a drug; the subsequent linkage makes it an adverse (or positive) drug reaction. The most familiar mechanism is the informal system in which physicians spontaneously report observed real or suspected adverse drug reactions to the manufacturer of the drug involved, to the FDA directly, or to their peers at meetings or in journals. Other activities include data collection centers that concentrate on organ systems (such as the eye or the kidney) or on events occurring within a particular health care delivery network (such as a group of hospitals). This network of activities has been reasonably effective in detecting those side effects that have caused the most significant public health concerns in recent years.

The second type of postmarketing surveillance is directed toward monitoring specific drugs. That is, the observation begins with the drug and looks ahead to the patient using it, for the purpose of linking the drug to patient injury or benefit. The FDA has employed this type only in special cases, by requesting the drug sponsor to establish a formal system of case-study surveillance over a specified number of patients who used the drug for a specified period of time. To date, no economical and universally applicable system for drug-specific surveillance has been developed. Although the concept has been discussed and studied by numerous groups, most particularly by the Joint Commission on Prescription Drug Use, the technology is still undeveloped. Its refinement to a degree that would afford broad application appears to be extremely time-consuming and expensive. Accordingly, use of this drug-specific approach will remain costly and in many cases not likely to justify the expense. Such a system may appropriately be used, however, when questions concerning adverse reactions exist that cannot be answered at all prior to approval or would delay approval for an unreasonable time. In any instance when formal drug-specific surveillance might be indicated, the potential informational and scientific benefits must be closely weighed against the financial and other costs of performing the surveillance.

It has been suggested that greater use of drug-specific postmarketing surveillance could be used to shorten the time that it now takes to develop a drug and have the drug reviewed by the FDA. The Commission does not agree with this perception. The statute that

governs drug approval requires that both safety and efficacy be established before a new drug is approved. Postmarketing surveillance does not substitute for the proof of safety and efficacy required to justify marketing a drug and therefore does not shorten the approval time.

- Because drug-specific postmarketing surveillance would generally not expedite NDA approval, it should only be required by the FDA in those individual cases when it is justified by the concerns raised by the drug involved. In all other cases, the FDA should continue to rely on the current systems of postmarketing surveillance to gather new information about a drug after NDA approval.

Postapproval Studies

In distinction to drug surveillance are drug studies which address expected questions regarding a drug that can be answered through a prospectively designed inquiry. After the safety and efficacy of a new drug have been sufficiently established to make the basic risk-benefit assessment and NDA approval decision, certain questions may still exist or specific additional information about a drug may be desirable. For example, what is the proper dosage in children or the elderly? Can it be used safely and with equal or greater efficacy with another drug commonly used in the same disease? Is the drug safe for use in pregnancy? In appropriate, carefully selected situations, carefully designed special studies would be helpful. These studies should not delay the approval decision; rather, they should be undertaken after the drug has been approved. These situations are not uncommon, but they should be handled individually. Each study should be developed prospectively by the FDA and the sponsor, taking into account the precise kinds of data being sought, the cost of the study, the probability of obtaining the information and the significance of the data to the public health.

- Special postapproval studies should be used to obtain specific information about a drug that is important but not critical to an NDA approval decision; the approval decision itself should not be delayed pending the additional data.

IV. FDA MANAGEMENT

INTRODUCTION

In looking at the management side of the drug review process, the Commission discussed a wide range of issues. An overriding theme was that current resources at the FDA are limited and not expected to increase in the foreseeable future. The first priority, thus, is to make better use of existing resources within the FDA. There is a serious need for an adequate and stable resource base, but within that base, functions can be streamlined and resources shifted. For instance, the Commission recommends that the Bioresearch Monitoring Program and the policies regarding generic drugs be reviewed and unnecessary activities eliminated so that significant FDA resources can be shifted to the task of reviewing important new drugs.

The nature of the relationship between the industry and the FDA is also seen to hamper an efficient and candid flow of information and decisions regarding INDs and NDAs. Attention should therefore be paid to improving lines of communication and to the prompt resolution of disputes.

The performance and productivity of the new drug approval process -- the ultimate concern of the Commission and its creators -- must be assessed on a more continuous basis. The Commissioner should have access to timely information on individual NDAs to ensure that productivity standards are being met, as well as useful data on the overall functioning of the drug review process.

Finally, it is necessary that the FDA have access to resources from outside the agency and that its interactions with drug sponsors be conducted so as to facilitate the review process. It is perceived by many that current stringent interpretations of the conflict-of-interest statute impede the FDA's ability always to have access to the best qualified outside expert advice. Accordingly, the problems surrounding this law need to be addressed.

A. RESOURCES FOR THE NEW DRUG REVIEW PROCESS

The Need for Adequate and Stable Resources

The Commission believes that the drug approval process is probably the single most important public responsibility assigned to the FDA. This conclusion agrees with recent FDA surveys of consumer groups, FDA management, and members of the various industries that the FDA regulates; all place drug review among the most critical agency functions.

The continuing adequacy of the FDA's personnel resources for meeting its new drug review responsibilities remains a source of concern and controversy. In 1962, Congress gave the FDA 180 days to act on each NDA. This provision expressed the legislative intent about the delays in the public's access to new drugs that were justified to permit the premarket review of these products. It is now up to Congress and the President to ensure that the FDA always has sufficient numbers of personnel in light of the INDs and NDAs submitted to comply as closely as possible with the law's mandate.

Adequate levels of resources are of no avail, however, if other restrictions interfere. For example, statutory ceilings on pay for physicians make recruiting difficult, particularly when other government agencies (such as the Veterans Administration) are allowed to pay more. In a similar vein, it hardly serves the public interest when the new drug approval process is delayed because of inadequate clerical or other support services. Funds to enable the temporary use of outside resources, when such help is necessary, should be available to ensure that necessary documents are promptly prepared.

The supply of resources must also be stable. Over the last decade, the FDA has been affected by government-wide freezes on hiring, promotion, and compensation. Turnover of personnel has created gaps in staffing levels and has frequently disrupted the drug review process. Additional factors, such as restrictions imposed on travel, advisory committees, and the use of contractors, have also on occasion forced drug regulatory decisions to be postponed for months while the administrative procedures were being straightened out.

Obviously, the new drug approval process is part of the government and is subject to changes in national policy. But the Commission recommends that the IND and NDA system be insulated in the short term from department-wide or government-wide edicts whose effects on the drug review system are not considered in advance. Given even a reasonably brief amount of time without the constraints of freezes, the FDA can be expected to absorb reductions in budget or personnel through adjustments in other, less critical programs while continuing the reviews of INDs and NDAs without interruption.

These various resource limitations hamper the FDA's productivity seriously, and this situation will continue unless steps are taken to enable the FDA to recruit and retain the needed numbers of highly qualified personnel, including senior administrative and professional review personnel and vital support personnel.

- Congress and the Administration should ensure that the FDA has sufficient and stable resources to review and act promptly on INDs and NDAs.

In the current economic situation, the FDA will probably not soon receive significant numbers of additional personnel. Accordingly, it will be essential that the FDA make the most efficient use of its present resources within the IND and NDA review process if performance there is to be significantly improved. Many of the recommendations of this Commission would serve to reduce the workload in certain areas, for example, by the appropriate modifications of the IND process and the rationalization of NDA requirements and review procedures.

If these changes are insufficient to guarantee the resources required for the drug approval process, the reassignment of persons or positions from other areas within the agency should be considered. Without attempting to review the entire range of FDA activities, the Commission has identified two areas directly related to activities regarding INDs and NDAs from which, through changes, resources might be reallocated: the Bioresearch Monitoring Program and the NDA requirements for generic versions of marketed drugs. The changes discussed below could serve both to release personnel who can be

immediately transferred to IND and NDA reviews and to open up positions that can, through attrition and hiring policies, be reassigned to the drug approval process. The Commission urges that any savings be applied directly to IND and NDA reviews.

Bioresearch Monitoring Program

The FDA Bioresearch Monitoring Program evolved out of a series of Congressional hearings from 1975 to 1977 that dealt with serious deficiencies in animal and clinical drug studies and questioned not only the studies cited, but also integrity of the entire research process. One purpose of the Bioresearch Monitoring Program, therefore, is to increase the quality of, and the level of confidence in the integrity of, all important data submitted to the FDA in support of INDs and NDAs.

Quality assurance is the primary mechanism by which the program objectives are to be achieved by building procedures into the research process to minimize errors and the possibility that an undetected error will influence the final results. Quality assurance is the focus of a series of regulations relating to both preclinical and clinical studies. These regulations set forth performance standards for the research process, but appropriately do not instruct how to meet these standards. The Good Laboratory Practices (GLP) regulations apply to nonclinical testing. Requirements regarding IRBs have also been established. Regulations describing the obligations of clinical investigators and of sponsors of clinical investigations (collectively referred to as Good Clinical Practice or GCP regulations) were proposed in 1977 and 1978; to a large extent, these merely restated existing regulations, but they also created new requirements in response to the Congressional revelations; these proposals have not yet been made final.

Taken together, the Bioresearch Monitoring Program regulations affect many areas of drug research, from standards for animal husbandry to ethical reviews by IRBs, and include record-keeping requirements to document compliance with the standards as well as quality assurance audits of study performance to assess compliance.

The Bioresearch Monitoring regulations warrant serious reanalysis in light of the FDA's experiences since 1978. Those requirements that have not proved integral to the quality assurance system should be eliminated. The Commission also recommends that, pending this review, only those portions of the GCP regulations that do not impose new requirements (i.e., those that merely recodify present obligations) be adopted at this time. The long delay in acting on the proposals for additional requirements strongly suggests that the FDA recognizes no compelling need for the new rules.

In particular, the record-keeping demands on clinical investigators and IRBs should be closely studied for justification and reasonableness. These participants in the research process, especially those in the academic world, have limited resources. For them, an increase in paperwork cannot be accommodated by an increase in clerical help; rather, it means that less research work will get done because more time must be devoted to documentation. It is also true that, although commercial research operations may be better able to absorb the increased costs resulting from the Bioresearch Monitoring regulations, they too are affected adversely. No one disputes that good science requires good records and that part of the performance of high-quality clinical research is keeping adequate records of studies. Every effort must be made, however, to keep the requirements for record keeping to the minimum critical to ensure the fundamental scientific value and reliability of the data generated. Requirements beyond this level burden scarce scientific resources unnecessarily.

The FDA should also work with appropriate bodies of experts outside the government to develop an educational program for clinical investigators, IRBs, and other participants in the research process to explain the purposes of the Bioresearch Monitoring Program, the objectives of regulatory requirements, and the role of the FDA and others in inspections and record audits. This cooperative effort could provide documents written in a style familiar to clinical scientists and other individuals not intimately involved in FDA's regulatory system. This program could also develop manuals, sponsor workshops at society meetings, and provide feedback in a number of ways, such as with a "hot line" to answer questions. This measure would foster an atmosphere of greater acceptance and compliance by the research community, conserve FDA resources in ensuring compliance, and save time and avoid misunderstandings on the part of those regulated by the Bioresearch Monitoring Program.

- In order to preserve scarce scientific resources, the Bioresearch Monitoring Program regulations should be reanalyzed, and requirements not critical to protect the integrity of the research process or justified by continuing regulatory problems should be eliminated.

A second major element of the Bioresearch Monitoring Program -- and the most resource-intensive for the FDA -- involves inspections of those participating in preclinical and clinical investigations to evaluate their compliance with the regulatory standards and the reliability of the quality assurance monitoring system. FDA investigators visit the study site and review in detail the records of the laboratory or investigator; they also travel to the offices of the sponsor or IRB for record audits. Inspection targets are selected by the direction of the Bureau of Drugs based on the importance of particular studies to a pending NDA ("routine surveillance" inspections) or by the FDA when it has reason to suspect problems ("for-cause" inspections).

These inspections take from one day to several weeks to complete, depending on the reason for the investigation, the size of the organization being inspected, and the level of compliance found. Following each inspection, the FDA inspector prepares a written report of his observations. If no serious problems are detected, the FDA will inform the party inspected that no action is required or that voluntary action is indicated to correct minor deficiencies. If a particular study is found seriously flawed, it may be rejected from future consideration by the FDA for an NDA. If certain serious and pervasive deficiencies are found with a clinical investigator, a laboratory, or an IRB, the party can be disqualified from serving further in the IND research process. Data received from a disqualified party cannot be used in support of any IND or NDA without additional validation.

The costs and benefits of this inspection program should be reviewed. Of 1032 inspections completed by the FDA in its last fiscal year, only 3% disclosed deviations from the regulations that were sufficient to warrant official action (such as rejection of a study or disqualification of the investigator). These

inspections included both routine surveillance and for-cause inspections, and presumably a higher percentage of problems were found in the for-cause audits. This 3% rate of detected noncompliance is approximately half that seen by the FDA in food processing or drug manufacturing plant inspections. Another 15% involved deviations justifying a formal FDA request for voluntary improvements in operation. From these data, it appears that the number of FDA routine surveillance inspections could be reduced, with inspections targeted more productively. The Commission recommends that the FDA review its accumulated data, particularly regarding routine surveillance inspections, on compliance among various groups of participants and revise the frequency of its inspections appropriately, the intent being to reduce the overall number without reducing the intensity of inspections in areas of significant noncompliance.

The reason for surveillance inspections is to detect any breakdown in the quality assurance system. Serious problems, however, can often be recognized within the first day of inspection. The Commission therefore recommends that the FDA develop a short form for use by its inspectors when conducting routine surveillance inspections to assess compliance with FDA Bioresearch Monitoring regulations. Such a form, perhaps analogous to that used by the FDA for food inspections, should be able to be completed within an eight-hour working day. If by that point the data appear sound or only minor problems are found that do not affect the quality of research or the protection of research subjects, the inspection should stop. Obviously, inspectors who are more knowledgeable and experienced in the area of scientific research will be better able to make these assessments promptly. Inspectors should not have to write a full report if no important violations are found. If the inspection leads to a suspicion of dishonesty or important deficiencies, the inspector should, of course, stay as long as necessary to resolve the problem.

During inspections, the FDA may also audit data from specific studies. The studies to be audited are usually chosen at random (except where the inspection is for cause) and may involve drugs that the sponsor is no longer developing. As noted earlier, only about one drug in ten ever reaches the NDA stage. It seems wise, therefore, to focus resources on that 10% and concentrate on drug products that are in or have

completed clinical development trials. (Of course, the study chosen for a specific drug may be a completed preclinical or early clinical study, when appropriate, rather than a clinical development trial.) By targeting inspections to drugs that are still moving toward market, the overall quality assurance procedures can still be assessed while at the same time providing further information meaningful for NDA decision making.

- o FDA inspections done under the Bioresearch Monitoring Program should focus on policies and procedures that produce the highest yield for the effort invested. For purposes of routine inspections, a short form should be developed.

NDA Requirements for Generic Drugs

At present, manufacturers of generic versions of drugs previously approved for marketing are themselves subject to FDA preclearance through the NDA process. Prior to 1962, the FDA did not generally compel generic products to be subject to separate NDAs. When Congress enacted the Drug Amendments of 1962, it instructed the FDA to review the drug products for effectiveness that had been earlier reviewed for safety as new drugs under the 1938 Federal Food, Drug, and Cosmetic Act. In carrying out this process, the FDA declared that generic versions of prescription drug products, like the pioneer (i.e., original) version, were subject to NDA requirements. Since then, the agency has also required each generic copy of post-1962 prescription drugs to be covered by a separate NDA as well. (Nonprescription drug products were to be regulated under the over-the-counter drug review program.)

Several generic drug manufacturers have contested the FDA's legal authority to require an NDA for a generic drug that merely copies a pioneer drug. This issue is now pending before the Supreme Court, and the Commission takes no position on the legal aspects of that case. But the Commission does believe that public policy should require preclearance. The simple fact that two products contain identical amounts of the same active ingredient is not sufficient to protect the public health. The United States has learned -- from experiences with pioneer and generic drugs alike -- that changes in formulation, manufacturing processes, or other factors can also cause safety and efficacy

problems. For example, the Elixir Sulfanilamide disaster, which killed over 100 people in 1937, involved a standard dose of a widely used sulfa drug, but it was mixed with an "inactive" ingredient, diethylene glycol, that proved to be highly toxic. More recently, the safety and effectiveness of different products containing identical quantities of digoxin varied as a result of the fact that they were absorbed into the body at different rates and to different degrees, depending on the excipients in the products and the tableting machines used.

- All prescription drug products, including generic versions of pioneer products, should be subject to premarket approval by the FDA for the protection of public safety.

The FDA's requirement that generic versions of drugs marketed before the Drug Amendments of 1962 have individual NDA approval would not have been feasible if the FDA insisted on a full NDA -- complete with preclinical and clinical studies on safety and efficacy -- for each product. As many as thirteen generics were being sold for every pioneer NDA product, and full NDAs would impose impossibly great burdens on manufacturers, the clinical research community, and the FDA. Accordingly, the FDA developed a short-form application, the Abbreviated NDA (ANDA). The central difference between NDAs and ANDAs is that an ANDA need not contain the detailed scientific data required in an NDA; instead, the sponsor must demonstrate the equivalence of its product to the pioneer and the ability to manufacture that product with consistent quality.

For reasons of history alone, however, the ANDA policy is not applicable to generic versions of pioneer drugs approved after the Drug Amendments of 1962. The sponsor of one of these products must submit a full NDA that includes the reports necessary to establish the safety and effectiveness of the generic drug. The FDA of course must review the material submitted, a time-consuming task.

This Commission was charged with identifying ways in which the new drug approval process could be accelerated without compromising the public safety. From that perspective, the Commission believes that extending the ANDA procedure to post-1962 drugs would free up key agency scientists so that they could focus

on the evaluation of truly novel drugs. The FDA currently expends significant drug review resources on evaluating full NDAs for generic drugs. Unlike ANDAs (which are reviewed almost entirely by chemists and biopharmaceutical experts), NDAs contain preclinical and clinical data that can only be reviewed by medical officers and pharmacologists. According to the Bureau of Drugs, generic NDAs accounted for 50.2% of all NDAs submitted between January 1974 and December 1980. Although the review resources allocated to them are much smaller than 50% (because the basic safety and efficacy questions with respect to the active ingredient have already been answered), NDAs for generic drugs still may consume a significant amount of medical officer and pharmacologist review time. For generic versions of post-1962 drugs that have been marketed sufficiently to confirm their profiles of safety and effectiveness, eliminating the requirements for safety and efficacy data in NDAs would reduce the workload of these critical scientific personnel. In these situations, a full NDA is not necessary to protect the public from the potential risks posed by a generic drug which relate to the quality of the product and its equivalency to the pioneer drug rather than to the safety and effectiveness of the active ingredient.

At the same time, the Commission recognizes that extension of the ANDA procedure to post-1962 drugs involves important considerations beyond the speed of the approval process. In eliminating most requirements for scientific data on generic drugs, the FDA would be making decisions based upon information ultimately derived from the data generated by the sponsor of the pioneer drug. These data represent a substantial investment of time and money by the originating party, and their use without compensation for the benefit of a competitor raises serious questions of equity and the incentives for future innovation in the pharmaceutical industry. It has been argued, for example, that a modification in the NDA/ANDA policy for post-1962 drugs could trigger profound changes in business planning and investments in research and development, particularly in situations in which a drug is off patent or the patent life of a drug has been substantially shortened by regulatory delays in the drug approval process. The argument, if correct, means that these changes would in the final analysis alter the rate and direction of pharmaceutical research and development.

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This Commission was not mandated to explore these consequences from a shift from NDAs to ANDAs for post-1962 generic drugs, nor was the Commission equipped with the expertise to undertake these inquiries. The central issue, incentives for innovation, is complex and may significantly affect the overall quality and cost of health care. It deserves serious evaluation. If it is concluded, however, that allowing ANDAs for post-1962 drugs will adversely affect the incentives for innovation, the Commission believes that this problem should be remedied in a direct fashion. Perpetuating regulatory requirements for a full NDA for generic products may protect incentives, but it serves no immediate public health purpose, is not scientifically justifiable, and may lead to unnecessary and ethically questionable human experimentation.

- o NDA requirements for generic versions of drugs originally approved after 1962 should be studied for the purpose of reducing the workload of NDA reviewers, particularly medical officers. The conflict between eliminating requirements that are not essential for the protection of public health, such as a full NDA, and ensuring the adequacy of economic incentives for drug innovation through appropriate mechanisms should be promptly addressed.

As stated earlier, generic versions of a product should be shown to be equivalent to the pioneer drug. Generally the most persuasive evidence of equivalence is derived from in vivo bioavailability studies (which show, among other things, the rate and extent to which the active ingredient in the generic product is absorbed into the bloodstream) and in vivo bioequivalency studies (which compare the bioavailability of the generic drug to that of the pioneer drug). The case of digoxin cited above showed that bioavailability problems can present serious public health risks.

Currently, the FDA requires in vivo bioavailability (and, for generic drugs, bioequivalency) data on all drugs originally approved after 1962, except when this is not technically possible or is unnecessary or inappropriate for the drug in question. For some generic copies of pre-1962 drugs, however, the FDA has waived the bioavailability and bioequivalency

requirements as being wasteful of scientific resources and not sufficiently cost effective. In establishing NDA requirements for generic versions of post-1962 drugs, the FDA should, in the Commission's opinion, adhere to a policy of requiring in vivo bioequivalency for these products.

There remains the question of how similar the various marketed versions should be to each other to minimize the chances for harm to patients. Present policy is that a generic version should show an absorption pattern within a range (for example, 20%) of the pioneer version. However, this would allow versions on the market that, if interchanged, could result in a significant difference in performance, considering the possibility that a patient may receive the best absorbed version on one occasion and the least absorbed on another. The Commission believes that there should not be a uniform policy for all drugs in this regard. It is neither possible nor wise to create a single standard for similarity for all drugs. Decisions on how much variance in bioavailability is permissible should be made individually for each case by experts who can judge how similar the versions should be to avoid both undertreatment and toxicity. Once this decision is made, then the kinds of data required to meet the established requirement can be determined by biopharmaceutical experts and statisticians.

- The FDA should require in vivo bioequivalency testing for all generic versions of drugs originally approved after 1962, except where clearly unnecessary or technically impossible.

B. IMPROVING INTERACTIONS WITH INDUSTRY

Agency-Industry Relations

A natural tension exists in the relationship between the regulators and the regulated. Nevertheless, a formal, distant relationship with infrequent contact is often not conducive to the prompt resolution of issues. Delays, wastes of agency and sponsor resources, and avoidable disputes can occur during the review process through the failure of principals to communicate efficiently and responsibly. Yet current agency standards of conduct operate frequently to compel a high degree of formality on the part of the FDA.

Designed to prevent undue influence on agency decision-making by nonagency personnel, these rules appear to mandate extensive documentation of contacts and the use of written, rather than oral, communications whenever possible. The drug review process would move more quickly if the relationships between the FDA and industry were improved and informal communications were encouraged to deal with those problems that do not require formality.

The FDA Commissioner has already undertaken steps to engender a more constructive environment for the review process. These actions are mandatory, but room for further improvement exists. The Commission recommends that the FDA provide guidance to the reviewing staff specifically to ensure that telephone discussions and informal meetings with industry personnel are effectively utilized to make the review process more efficient. Documentation should, of course, continue when the nature of the information justifies it. Sponsors should be discouraged from seeking meetings with busy review personnel on unimportant issues or from trying to obtain progress reports that can better be obtained by other means.

On the other hand, FDA review personnel should initiate telephone discussions or personal meetings whenever that would expedite the consideration of significant issues. The agency staff should take an active role in the early identification and prompt resolution of questions. Formal, written communication slows down the interchange, involves the FDA's overburdened clerical resources, and discourages candid exchanges. Of course, written correspondence should be used when it bears substantively on the NDA or IND review.

- The FDA should provide guidance to its staff to encourage all review personnel to conduct timely, forthright, and even-handed discussions with sponsors of the significant issues that arise at any time during the IND and NDA review process. An atmosphere of mutual respect and professional conduct should be encouraged and maintained. Formal communications should be limited to situations where such formality is warranted.

Resolution of Disputes

The Commission also recognizes that disputes are inevitable between regulators and the regulated. Some disputes may be administrative or procedural, while others may involve basic questions of good science. They may be minor conflicts over aspects of a drug's labeling or profound disagreements over difficult risk-benefit assessments. Regrettably, in many instances, such disputes seriously hold up the review process because they cannot be resolved.

Mechanisms do exist within the FDA for handling disputes, but they usually require significant time to invoke and obtain an answer and are not fully utilized. The present system relies on ad hoc intervention by senior management and thus is neither prompt nor consistent.

Conflict-resolution mechanisms should seek to attain the various different objectives of each party who may become involved in a dispute. Drug sponsors, for example, need a prompt answer; if it takes seven months to decide whether a new six-month study is required, it is faster to do the work. It takes time, of course, to arrange a meeting, assemble documents, make a presentation, and deliberate an answer, but excessive requirements for written materials can delay decisions much longer. Sponsors also want a definitive answer; equivocal answers may necessitate further negotiations and new conflicts. Sponsors seek a forum that will be fair and objective in evaluating both sides of the dispute; if a supervisor feels compelled always to support a subordinate, appeals from a decision of the subordinate are futile. Finally, sponsors must be confident that regardless of the outcome of the dispute, agency employees will not retaliate for the sponsor having "gone over their heads." Unfortunately, many in industry today fear the possibility of such a delayed punishment. In a system as complex as the NDA approval process, opportunities exist for retaliation, and the potential for perceptions of retaliatory behavior is even greater. It is imperative, therefore, that the integrity and professionalism of the FDA reviewers be supported and assured.

FDA employees involved in a conflict with a drug sponsor also have needs with regard to appeal and resolution procedures. The system should be fair and objective to FDA personnel as well as to sponsors.

Professionals cannot expect uniform agreement from supervisors and colleagues, but they are entitled to a respectful hearing. And subordinates should also be able to use the appeal mechanisms when, for example, they feel that a conflict was wrongly resolved.

FDA management has its own requirements for a conflict-resolution process. First, it must preserve line responsibility; no manager likes to learn about a problem in the manager's area from the boss. The system must also respect lines of authority; except in rare cases, the final decision should be made by the official who has been charged with responsibility for that matter. Sound management principles suggest that disputes should be resolved at the lowest levels possible, that only issues ripe for decision should be appealed, and that routine operations should function well enough that policies are clear and conflicts rare. The resources and energies devoted to disputes should be limited; if a manager becomes a full-time arbitrator, management is impossible.

The public, too, is entitled to certain expectations in an appeals mechanism. It wants a prompt and efficient resolution of disputes, but it also wants answers that comport with the larger public policy objectives that regulation is intended to serve.

Against this backdrop, it should be possible for the FDA to develop several mechanisms for conflict resolution, tailoring them to different types of disputes. The Commission recommends that disputed issues be defined at the level at which they emerge and be resolved at the lowest possible level of line management with as little formality as necessary. When this approach fails, the sponsor should have ready access to the resolution mechanism most appropriate to the dispute. Specifically:

(1) An ombudsman function should be established in the Commissioner's Office to deal with administrative or procedural issues that arise in the review of INDs or NDAs for which the intervention either of FDA top management or of an advisory committee would be unwarranted. The ombudsman function would be appropriate to mediate problems such as the failure of reviewers to provide timely responses to questions, the inability of companies to schedule needed meetings, difficulties in obtaining minutes of meetings, or a failure to meet time schedules. In carrying out these duties, the

ombudsman function would work directly with the involved FDA employees and their immediate supervisors. It would also advise FDA management of persistent problem areas.

(2) Major substantive issues requiring scientific judgment (such as the interpretation of data or the significance of a finding) may best be resolved through the intervention of a disinterested expert body. The FDA currently refers certain matters to its standing advisory committees, but drug sponsors are not entitled to have disputes submitted to these committees. In the future, either the FDA or the sponsors should be able to have disagreements brought promptly before an appropriate standing advisory committee (or other outside experts), who would recommend a basis for resolution to the FDA.

(3) Policy issues, whether scientific, regulatory, or other, may require the involvement of senior FDA management. More use should be made of the existing procedures for timely referral of such issues to the Office of the Commissioner when they cannot be satisfactorily resolved at a lower level. Sponsors should clearly appreciate, however, that it is not in their own best interest to pursue trivial or inappropriate issues at this level, and the FDA should retain the right not to hear such appeals if, in the Commissioner's opinion, the correct decision has been rendered at a lower level.

- The FDA Commissioner should encourage the timely and equitable resolution of disputes regarding INDs and NDAs by ensuring that mechanisms appropriate for different types of disputes are in place and readily accessible. In particular, the Commissioner should expand on existing mechanisms and explicitly encourage their use. An ombudsman function should also be established in the Commissioner's Office, where administrative or procedural problems can be taken when they cannot be satisfactorily or promptly resolved with line management.

C. TRACKING THE REVIEW PROCESS TO ENSURE TIMELINESS

As chief executive officer, the FDA Commissioner has ultimate responsibility for the quality and timeliness of decisions made by the FDA. The Bureau

of Drugs and the Office of New Drug Evaluation are responsible for the day-to-day management of the review operations, but the Commissioner is ultimately responsible for seeing to it that appropriate productivity standards are set and met. To perform this function effectively, the Commissioner must have access to timely, accurate information on the status of all drugs under review.

The Bureau of Drugs currently utilizes a computer-based tracking system to monitor and coordinate reviewer assignments and task completions. The Commission believes that, in addition, a simple, cost-effective tracking system should be established to enable the Commissioner and other agency managers, as well as those responsible for FDA oversight, to determine the progress of reviews of individual NDAs and to assess the overall performance of the NDA review process.

Such a system would make it possible to determine immediately the precise status of any NDA, to review the workload and productivity of individual employees, review teams and divisions and even drug sponsors, and to monitor the overall efficiency of the drug review process. Reports from the system should highlight cases of long delays or possibly inadequate resources. If instances of delays or problems become apparent, managerial efforts can be promptly directed to overcoming the difficulties holding up action.

- The FDA Commissioner should be provided with timely information on the status of NDAs undergoing review. Toward that end, a computer-based system for tracking NDAs should be utilized to enable the Office of the Commissioner, as well as senior Bureau of Drugs management, to review regularly the status of NDAs and to report appropriate information to the Commissioner.

D. CONFLICT OF INTEREST AND EXPERT ADVISERS

Since the early 1970s, the FDA has drawn on experts from the scientific communities in academia and government for members of its advisory committees. These committees are of crucial importance to the FDA, not only in the evaluation of new drugs, but in developing guidelines for testing, reviewing new data

about marketed products, classifying devices, and reviewing over-the-counter drugs and licensed biological and blood products. It is imperative that the FDA have expert advice that is of the highest quality.

Elsewhere in this report, the Commission recommends increased use of outside experts throughout the IND and NDA process. This step will undoubtedly mean that more experts will be needed by the agency. A major constraint on the quantity as well as the quality of outside expertise available to the FDA is the conflict-of-interest restrictions imposed on the agency and its advisers.

According to the federal conflict-of-interest statute (18 U.S.C. § 208), government employees are prohibited from participating in decisions in which they have a financial interest. In addition to full-time federal employees, the statute also applies to Special Government Employees (i.e., part-time advisers, including the FDA's advisory committee members). Government employees must disqualify themselves from participating in any "particular matter" in which they, a spouse or minor child, their place of employment, or an organization in which they hold office has a financial interest. Violation is punishable by a fine of up to $10,000 and up to two years' imprisonment. The FDA Commissioner, however, is empowered to exempt employees whose financial interests are not "so substantial as to be deemed likely to affect the integrity of [their] services."

The FDA screens all advisory committee appointees for possible conflicts of interest by reviewing their financial interests (including investments, income, and research grants or contracts) that derive from any company that makes or sells an FDA-regulated product. Because it has been difficult to rely exclusively on experts who have no financial ties to any regulated company, the FDA has on occasion appointed advisers with such an interest but has imposed additional requirements: Financial interests exceeding $5,000 must be publicly disclosed before appointment, and no individual may participate in a decision related to a company in which the expert's financial interests exceed $1,000. In addition, the FDA Commissioner has on occasion waived the requirements in instances where the agency's need for the particular expert was very important. But it is apparent that the FDA does not want to overuse this authority.

True conflict of interest must clearly be avoided by the FDA in its use of expert advisers, both for legal reasons and to prevent perceptions by the public of improper influence on the agency by the industry. On the other hand, excessive constraints on the use of outside experts can hinder the FDA's ability to conduct its mission in optimal fashion -- especially when the critical statutory language calls for the judgment of experts. While prohibiting committee members from participating in the discussion on specific drugs on which they have worked is easy to apply, the Commission questions its logic. An individual investigator may conclude that a drug has merit or not on the basis of personal experience, and a competent investigator's opinion should be of value to a committee deliberating the drug's approvability. Furthermore, on some occasions, the FDA has had to rely on such expert opinion when it was not possible to constitute a committee that lacked personal experience with the drug in question.

In 1977 and 1978, the General Accounting Office and the Oversight and Investigations Subcommittee of the House Commerce Committee questioned several instances in which FDA advisers who had indirectly benefitted or appeared to benefit from research monies from drug sponsors had participated in advisory committee discussions of regulatory issues affecting products made by these companies. The FDA had ruled that, although outside advisers could not participate in discussions regarding a specific product which was made by companies from which they had received research funding (even when the research was unrelated to the product under review), they could participate in discussions regarding a class of products, one of which was produced by the sponsor of the adviser's research. The FDA believed that a true conflict of interest occurred only if an adviser's recommendation could lead to a competitive advantage or disadvantage for the specific company from which the adviser had received financial support. When this position was questioned by the GAO and the Congressional Subcommittee, the FDA sought clarification from the Department of Justice.

The Department of Justice ruled that the possibility of a competitive advantage or disadvantage was not a prerequisite for conflict of interest. Referring back to a 1963 Presidential Memorandum, the Justice Department concluded that any direct and

predictable effect on financial interests that might result from the action being discussed by the advisers sufficed to establish conflict of interest. The Department reasoned that any decision that could affect the drug sponsor might also affect the continuity of an adviser's research support. In one of the specific examples referred to the Justice Department by the FDA, the committee member had no financial connection with any manufacturer but was in a line of business that relied on one of a group of products being discussed. The Justice Department would have him disqualified from any deliberations affecting the entire group of products. In another case, conflict of interest was declared to exist even for an adviser who himself had not received research funding from the company whose product was under review, but whose university had. The issues surrounding the Department of Justice ruling are examined at greater length in published papers.8/

The 1978 Justice Department ruling needs modification in order to guarantee that the FDA has access to the most qualified and respected experts in this country. Accordingly, the FDA Commissioner should request the Department of Justice to reevaluate the conflict-of-interest statute and render an interpretation that strains less to find credible situations of potential conflict of interests.

The Commissioner should also make greater use of his waiver authority. Frequent exemptions from conflict-of-interest restrictions may be criticized, but the proper use of this power by a Commissioner who seeks to avoid both improper outside influence and the rejection of qualified advisers is surely in the public interest.

8/ Merrill, R.M.: "Problems Involving Federal Conflict of Interest Restrictions on Members of FDA Advisory Committees and Agency Officials." Center for the Study of Drug Development, PS 8032, Rochester, N.Y., April 1980.

Vodra, W.W.: "'Conflict-of-Interest' Restrictions on Government Employees and Part-Time Expert Advisors." Appendix X, Report of Joint Commission on Prescription Drug Use, January 1980.

- Barriers to the participation of the best qualified outside expert advisers in the drug approval process must be addressed. In particular, the FDA Commissioner should request from the Department of Justice a less restrictive interpretation of the federal conflict-of-interest statute than that issued in 1978.

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